zilucoplan solution for injection in prefilled syringe (Zilbrysq®)

UCB Pharma Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the orphan equivalent medicine process

zilucoplan (Zilbrysq®) is accepted for restricted use within NHSScotland.

Indication under review: 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.

SMC restriction: for adult patients with refractory anti-AChR antibody positive gMG if:

- the disease has not responded adequately to corticosteroids and at least two other treatments including non-steroidal immunosuppressive therapies (NSISTs) and rituximab, or these options are contraindicated or not tolerated, and
- the disease is uncontrolled, as defined by a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of six or greater or a Quantitative Myasthenia Gravis (QMG) score of 12 or greater, and
- patients are being considered for, or treated with, maintenance intravenous immunoglobulin (IVIg) or plasma exchange (PLEX).

In a double-blind phase III study, the addition of zilucoplan to standard therapy was associated with a statistically significant reduction in patient-reported myasthenia gravis symptoms and their effects on daily activities compared with placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Zilucoplan inhibits the effects of complement protein C5, resulting in decreased cytolytic activity of the membrane attack complex (MAC), and prevents the assembly of MAC. The recommended dose of zilucoplan is 16.6 mg (less than 56 kg body weight), 23 mg (56 to less than 77 kg) or 32.4 mg (77 kg or greater) subcutaneously (SC) once daily.[1]

1.2. Disease background

Generalised myasthenia gravis (gMG) is a rare, chronic, autoimmune condition caused by pathogenic immunoglobulin-G (IgG) autoantibodies binding to acetylcholine receptors or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction, causing failure of neuromuscular transmission. This leads to debilitating and potentially life-threatening muscle weakness. MG is more common in women than in men and can affect people of all ages. Approximately 80% of patients with MG are anti-acetylcholine receptor (AChR) antibody positive. In patients with undetectable autoantibodies, diagnosis is made through neurophysiological examination and successful trial of acetylcholinesterase inhibitors. Symptoms are relapsing and remitting in nature, and common symptoms include drooping of the eyelids and double vision when muscles in and around the eye are affected, impaired speech and swallow associated with involvement of muscles in the face and throat, mobility issues when limb muscles are involved, impaired respiratory function with lung muscle involvement and extreme fatigue. A potentially life-threatening myasthenic crisis requiring ventilation because of respiratory failure can occur in up to 20% of patients.[2, 3]

1.3. Company proposed position

The submitting company has requested that zilucoplan is restricted for use for adult patients with refractory anti-AChR antibody positive gMG if:

- the disease has not responded adequately to corticosteroids and at least two other treatments including non-steroidal immunosuppressive therapies (NSISTs) and rituximab (for example: one NSIST and rituximab or two NSISTs), or these options are contraindicated or not tolerated, and
- the disease is uncontrolled, as defined by a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of six or greater or a Quantitative Myasthenia Gravis (QMG) score of 12 or greater, and
- patients are being considered for, or treated with, maintenance intravenous immunoglobulin (IVIg) or plasma exchange (PLEX).

1.4. Treatment pathway and relevant comparators

The aim of treatment for gMG is to induce remission or achieve minimal manifestations. Treatment options and combinations depend on MG subtype, symptoms, patient choice, comorbidities and response. Pyridostigmine is the most commonly used acetylcholinesterase inhibitor for direct symptomatic control. Most patients also receive long-term treatment with disease-modifying immunosuppressants; corticosteroids are used first line however if

contraindicated, a non-steroidal agent such as azathioprine, mycophenolate mofetil, methotrexate or ciclosporin may be considered as an alternative. These treatments can also be used in combination in slow responders, in patients who relapse or if underlying comorbidities would be exacerbated by a prolonged course of steroid therapy. Off-label rituximab can be used to treat patients that are refractory to conventional therapy, however lower response rates have been reported in some patients with AChR antibody positive MG compared with other biomarker subtypes. Surgical intervention with a thymectomy may be considered for patients with AChR antibody positive MG when symptoms have stabilised.[4, 5] Other medicines have been licensed for gMG, however, have not been recommended by SMC. IVIg or PLEX may be required to assist symptom control during steroid titration or to treat a MG crisis.

Experts consulted by SMC note that IVIg and PLEX are mainly used to treat acute exacerbations and are only used for maintenance therapy in a very small group of patients. Given the submitting company's proposed positioning, the most relevant comparators for this submission are maintenance immunoglobulin (IV or SC, in combination with standard of care), and, to a lesser extent, maintenance PLEX (in combination with standard of care).

1.5. Category for decision-making process

Eligibility for a PACE meeting

Zilucoplan meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of zilucoplan for the treatment of anti-AChR antibody positive gMG comes from RAISE. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study[3, 6, 7]

Criteria	RAISE
Study design	A multicentre, randomised, double-blind, phase III study.
Eligible patients	• Adults aged ≥18 years and <75 years. • Diagnosis of gMG at screening (MGFA disease class II to IV). • Positive serology for AChR binding autoantibodies. • MG-ADL score of ≥6 at screening and baseline. • QMG score of ≥12 at screening and baseline. • Four or more of the QMG test items must have been scored at ≥2 at screening and baseline. • No change in corticosteroid or immunosuppressive therapies for at least 30 days prior to baseline or anticipated to occur during the 12-week treatment period. • Received a quadrivalent or serotype B meningococcal vaccine, or both, at least 14 days before the first dose of study medicine.
Treatments	Patients were randomised to receive zilucoplan or placebo SC once daily for 12 weeks. Zilucoplan dosing was based on body weight: 16.6 mg (≥43 kg to <56 kg body weight), 23 mg (≥56 kg to <77 kg) or 32.4 mg (≥77 kg). All standard of care treatments for gMG were expected to be kept at the same dose throughout the

	study. Rescue therapy with IVIg or PLEX was permitted as per investigator's judgement.
Randomisation	Patients were randomised equally. Randomisation was stratified according to MG-ADL score (≤9 versus ≥10), QMG score (≤17 versus ≥18) and geographical region (North America, Europe and Japan).
Primary outcome	Change from baseline in MG-ADL score at week 12 in the mITT population (all randomly assigned patients who received at least one dose of study medicine and had at least one postdosing MG-ADL score). The MG-ADL is an 8-item patient-reported outcome measure assessing MG symptoms and their effects on daily activities. Each item in the scale is scored 0 to 3 (0 = none, 3 = severe disease) point scale. The total score is the sum of all individual item scores and ranges from 0 to 24. Higher scores indicate more severe disability due to MG. A decrease from baseline score indicates improvement.
Select secondary outcomes	Change from baseline at week 12 in QMG total score, MGC total score and MG-QoL 15r total score.
Statistical analysis	Type 1 error rate was controlled at a 2-sided alpha level of 0.05 using a parallel gatekeeping testing framework. Secondary outcomes were only tested if the primary outcome was statistically significant. The aforementioned secondary outcomes were tested in a fixed sequential manner and were tested in the order listed.

Abbreviations: AChR = acetylcholine receptor; gMG = generalised myasthenia gravis; IVIg = Intravenous immunoglobulin; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis-Activities of Daily Living; MGC = Myasthenia Gravis Composite; MGFA = Myasthenia Gravis Foundation of America; MG-QoL 15r = Myasthenia Gravis-Quality of Life 15-item scale revised; mITT = modified intention-to-treat; PLEX = plasma exchange; QMG = Quantitative Myasthenia Gravis; SC = subcutaneously

Zilucoplan in combination with standard of care was associated with a statistically significant reduction in MG-ADL score from baseline to week 12 compared with placebo. Key secondary outcomes were also statistically significant. See Table 2.2 for details.

Table 2.2. Primary and key secondary outcome results of RAISE (mITT population)[1, 3]

Outcomes: Change from baseline in total score at week 12, LS mean	Zilucoplan (n=86)	Placebo (n=88)	Zilucoplan change LS mean difference versus placebo (95% CI)	p-value[B]
MG-ADL[A]	-4.39	-2.30	-2.09 (-3.24 to -0.95)	<0.001
QMG	-6.19	-3.25	-2.94 (-4.39 to -1.49)	<0.001
MGC	-8.62	-5.42	-3.20 (-5.24 to -1.16)	0.002
MG-QoL 15r	-5.65	-3.16	-2.49 (-4.45 to -0.54)	0.013

[A] Primary outcome. [B] Analysis based on a MMRM ANCOVA model

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis-Activities of Daily Living; MGC = Myasthenia Gravis Composite; MG-QoL 15r = Myasthenia Gravis-Quality of Life 15-item scale revised; mITT = modified intention-to-treat; MMRM = mixed models repeated measures; QMG = Quantitative Myasthenia Gravis

RAISE-XT is a phase III open-label extension study evaluating the long-term efficacy and safety of zilucoplan in patients with gMG who had previously successfully participated in the RAISE study or the phase II study MG0009. All patients received zilucoplan 0.3 mg/kg SC once daily. At data cut November 2023, 200 patients had enrolled in RAISE-XT; median exposure to zilucoplan was 2.2 years; 73% were still enrolled in the study. In patients who had received zilucoplan 0.3 mg/kg in RAISE or MG0009, MG-ADL and QMG scores continued to improve until week 24. In patients who

received placebo in RAISE or MG0009, MG-ADL and QMG scores markedly improved at week 13 (the first week after switching to zilucoplan) and continued to improve through to week 24; these improvements were maintained in both groups through to week 120.[8]

2.2. Evidence to support the positioning proposed by the submitting company

Preplanned subgroup analysis was performed in a MG refractory subgroup; patients were considered MG refractory if they had treatment for at least 1 year with two or more of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, other immunosuppressive treatments, or history of treatment with at least one of these therapies for ≥1 year, and required maintenance PLEX or immunoglobulin (IV or SC) at least every 3 months for the 12 months prior to enrolment. The change from baseline at week 12 in MG-ADL score (modified intention-to-treat [mITT] population, MG refractory) was -4.89 in the zilucoplan group (n=44) and -2.26 in the placebo group (n=42).[3, 9]

2.3. Health-related quality of life outcomes (HRQoL)

The primary outcome (MG-ADL score) and key secondary outcome (MG-QoL 15r) of RAISE were patient-reported outcomes and have been reported in Table 2.2 above. Other patient-reported outcome measures were change from baseline to week 12 in Work Productivity and Activity Impairment: Specific Health Problem (WPAI: SHP) Questionnaire, EQ-5D-5L and Quality of Life in Neurological Disorders (Neuro-QoL) Short Form fatigue score. For WPAI: SHP, no differences were observed between treatment groups. For EQ-5D-5L visual analogue scales, numerically greater mean increases from baseline were observed at week 12 with zilucoplan versus placebo (8.97 versus 5.81). For Neuro-QoL Short Form fatigue score, the LS mean difference between zilucoplan and placebo numerically favoured zilucoplan (-3.06).[6, 9]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing zilucoplan with maintenance immunoglobulin or PLEX, the submitting company presented an indirect treatment comparison (ITC). Three network meta-analyses (NMAs) were conducted: a bivariate NMA, a two-stage baseline risk-adjusted and bivariate NMA and a conventional NMA. The bivariate NMA has been used to inform the economic base case and the two-stage baseline risk-adjusted NMA informs a scenario analysis; details of these NMAs can be found in Table 2.3.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	<u>Bivariate NMA</u> The bivariate NMA supports simultaneously analysing two potentially correlated outcomes across an intervention network, through information borrowing between outcomes when one network is sparse or missing data for a comparator of interest. In this analysis, QMG data were used to predict MG-ADL outcome, thereby allowing inclusion of IVIg and PLEX studies that reported QMG outcomes in the network. <u>Two-stage baseline risk-adjusted and bivariate NMA</u> This involved adjustment of the data for baseline risk using the mean placebo effect, followed by conducting the bivariate NMA.
Population	Adult patients with myasthenia gravis.

Comparators	Eculizumab, efgartigimod, IVIg, LPE, PAIA, PLEX, ravulizumab, rituximab and rozanolixizumab. The comparators of interest were IVIg and PLEX.
Studies included	18 studies (including RAISE for zilucoplan).
Outcomes	Change from baseline in MG-ADL score and MG-ADL response. MG-ADL response definitions varied across studies. In RAISE it was defined as a ≥3-point improvement at 12 weeks whereas in Bril et al 2024 (for IVIg) it was defined as ≥2-point improvement at 24 weeks.
Results	Zilucoplan and IVIg had similar response rates across both NMAs. Overall, the results suggest that zilucoplan performed better than placebo for both outcomes in the bivariate NMA, and for change from baseline in MG-ADL score in the two-stage baseline risk-adjusted NMA. There was no evidence to suggest a difference in efficacy for IVIg and PLEX when compared with placebo. However, the credible intervals were wide and therefore the results should be interpreted with caution.

Abbreviations: CFB = change from baseline; CrI = credible interval; IVIg = maintenance intravenous immunoglobin; LPE = lymphoplasma exchange; MG-ADL = Myasthenia Gravis-Activities of Daily Living; NMA = network meta-analysis; OR = odds ratio; PAIA = Protein A immunoadsorption; PLEX = plasma exchange; QMG = Quantitative Myasthenia Gravis; RCT = randomised controlled trial

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

Combined evidence from RAISE and MG0009 supports the relative safety of zilucoplan 0.3 mg/kg compared with placebo (both in combination with standard of care) for the treatment of patients with anti-AChR antibody positive gMG. No safety data are available comparing zilucoplan with the relevant comparators of the submission (maintenance immunoglobulin or PLEX). Safety data are also available from the RAISE-XT study however these are non-comparative. No safety data were provided for the subgroup relevant to the proposed positioning.

Safety analyses in the RAISE/MG0009 studies were performed in all patients who received at least one dose of study treatment. The mean duration of exposure was 82.0 days in the zilucoplan group and 81.7 days in the placebo group. Treatment-related adverse event (AE) were reported by 32% (32/100) of patients in the zilucoplan group and 26% (27/103) of patients in the placebo group. In the zilucoplan and placebo groups respectively, patients with a reported serious AE were 16% in both groups and patients discontinuing therapy due to an AE was 4.0% versus 1.9%.[3] In RAISE-XT (median duration of exposure 2.2 years), 2.5% (5/200) of patients taking zilucoplan had a serious treatment-related AEsin 2.5% (5/200).[8]

In RAISE and MG0009, the most frequently reported treatment-emergent AEs in the zilucoplan group and placebo group respectively were headache (16% in both groups), injection site bruising (14% versus 9.7%), diarrhoea (10% versus 2.9%), myasthenia gravis (10% versus 13%), injection site pain (8.0% versus 3.9%), contusion (8.0% versus 3.9%), urinary tract infection (7.0% versus 3.9%), amylase increased (7.0% versus 2.9%), lipase increased (6.0% versus 2.9%), nasopharyngitis (5.0% versus 2.9%) and peripheral oedema (5.0% versus 1.0%).[3]

Overall, regulators considered the safety profile of zilucoplan to be generally mild to moderate in severity and manageable. The most important risk is *Neisseria* infection which is a well-characterised consequence of C5-inhibition. The Summary of Product Characteristics (SPC) states that all patients must be vaccinated against meningococcal infections at least 2 weeks prior to the

start of treatment with zilucoplan and it is also recommended that patients initiate immunisations according to current guidelines.[1, 3]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Zilucoplan would be the first C5 inhibitor to be made routinely available in NHSScotland for the treatment of anti-acetylcholine receptor antibody positive generalised myasthenia gravis.
- Evidence to support the efficacy and safety of zilucoplan comes from RAISE, a double-blind phase III study. The addition of zilucoplan to standard of care treatment resulted in statistically significant benefits in the primary outcome and also in clinically relevant key secondary outcomes. The -2.09 point difference between zilucoplan and placebo in MG-ADL score is considered clinically meaningful. Results in the subgroup with refractory disease, which align with the positioning population, were consistent with the overall study population. For the key secondary outcome, change from baseline at week 12 in QMG, different minimal clinically important differences have been proposed in the literature, ranging from -2.6 to -3.0 points.[10-12] The -2.94 point difference between zilucoplan and placebo can also be considered clinically meaningful. Together, these outcomes demonstrate benefit from both the patient and clinician's perspective.[3]
- Zilucoplan is administered subcutaneously once daily and can be self-administered at home, which is a convenient route of administration for many patients.

4.2. Key uncertainties

- It is uncertain if data from RAISE represents the company's proposed position. Definitions of refractory disease between the study and the positioning are different, rituximab was not permitted within 12 months prior to baseline, and no patients were receiving immunoglobulin or PLEX at baseline. Furthermore, it is unknown how many patients were being considered for maintenance immunoglobulin or PLEX.
- There are no direct data comparing zilucoplan with maintenance immunoglobulin or maintenance PLEX. The ITC had several limitations: the population used in the ITC (adults with myasthenia gravis) was much broader than the licensed indication and proposed positioning; the relevant comparators, IVIg and PLEX, are not licensed for the treatment of gMG in this setting; sparse data were available for these comparators and low-quality observational studies were included in the analysis; there was variation between studies in terms of outcome definitions, assessment timepoints, study design, previous treatments and baseline severity; the PLEX studies did not assess MG-ADL outcomes so QMG results were used to estimate MG-ADL outcomes; there was high variability in placebo response rates; and the results had very wide credible intervals. Given these limitations, the results of the ITCs are highly uncertain.
- There are limited long-term data to support the efficacy and safety of zilucoplan. Randomised data are limited to 12 weeks which may be suboptimal; regulators

recommend a treatment period of 24 weeks to evaluate efficacy given that gMG is a chronic condition that fluctuates over time.[3] Data from RAISE-XT suggest that the treatment effect is maintained up to approximately 2 years[8], however these data are associated with some uncertainty since RAISE-XT is an open-label, non-comparative study.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that zilucoplan fills an unmet need for a small group of patients with inadequate disease control on currently available therapies. For this group of patients, clinical experts consider zilucoplan to be a therapeutic advance as an effective additional treatment choice with a different mechanism of action.

4.4. Service implications

There may be some service implications associated with the introduction of zilucoplan. Patients will require vaccination against meningococcal infections prior to initiation. As an add-on to standard treatments there will be increased clinical monitoring. However, as an alternative to maintenance immunoglobulin or PLEX, the self-administered SC injections of zilucoplan may have benefits for the service and patients.

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of zilcuoplan, as an orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Refractory generalised MG is a rare and chronic autoimmune disease that can have a substantial impact on the day-to-day lives of people living with it from a physical, emotional, social, psychological, and financial perspective. It is a fluctuating disease where some days are better than others. MG often affects the ocular muscles first, impacting vision, and can also affect other facial muscles making smiling, facial expressions, or chewing difficult. This can worsen and evolve into difficulty swallowing and breathing. Speech can also be affected and another disabling symptom is fatigue which can be very severe. It can have a negative impact on patients' social lives and increased feelings of anxiety, depression, fear, and reduced confidence. In addition, it is typical to see initial manifestations appear earlier in women than in men. This means that women tend to be diagnosed and treated for MG longer, and standard therapy options may affect factors related to women's health, such as fertility and family planning.
- Patients with refractory MG face persistent symptoms with severely limited treatment options and are at increased risk of myasthenic crisis, which can be life-threatening and often requires hospitalisation. Refractory patients are typically reliant on the chronic use of what should be rescue therapies such as IVIg and PLEX (in combination with other standard treatments). These treatments are invasive and resource-intensive, requiring clinical staff for administration and

monitoring, associated with serious risks, including thromboembolic complications and infection or vascular access issues, subject to global shortages, and disruptive to daily life, with patients unable to plan ahead due to unpredictable symptom control. IVIg and PLEX can only be delivered at a very limited number of hospitals in Scotland, which can be very disruptive for some patients. Even with access to these treatments, patients can still experience poor disease control. Ultimately, there remains a substantial unmet need for people living with refractory MG. These patients face limited options, ongoing risk of crisis, and a high burden from both the disease and its treatment.

- Zilucoplan is a targeted treatment option that has been shown to reduce both symptom and treatment burden in patients with gMG, with favourable tolerability, fast onset and sustained efficacy. It has the potential to improve the lives of patients with refractory disease, enabling them to regain independence, possibly reduce reliance on other medications, including corticosteroids, and return to activities they had previously lost, such as education or employment. Another key advantage of zilucoplan is that it is administered subcutaneously and can be self-injected at home. Home administration reduces travel, treatment time, hospital stays, and reliance on clinical staff, supporting better quality of life. Zilucoplan may also reduce the rate of emergency hospitalisations due to MG relapse or crisis. By reducing treatment burden and enabling patients to regain independence, zilucoplan addresses a critical unmet need in refractory MG and offers a clinically meaningful improvement in quality of life. Zilucoplan would be the first complement inhibitor to be made routinely available in Scotland.
- The substantial caregiver burden in MG arises from the physical, emotional, and financial consequences of the disease. Challenges include the stress of monitoring for choking or breathing difficulties, the need to accompany patients to hospital-based treatments, and the disruption to work and family life caused by unpredictable symptoms and treatment schedules. Zilucoplan offers a potential reduction in carer burden through symptom control. By helping patients achieve more consistent symptom management, the need for daily physical support may be reduced.
- PACE participants felt that zilucoplan should be used in patients with refractory disease where current available treatments have been ineffective, which is in line with the company's proposed positioning. Patients will need to be taught how to self-administer subcutaneous injections, although this should be a straightforward process.

Additional Patient and Carer Involvement

We received a joint patient group submission from Myaware and Muscular Dystrophy UK. Both organisations are registered charities. Myaware has received 11% pharmaceutical company funding in the past two years, including from the submitting company. Muscular Dystrophy UK has received 1.32% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from both patient groups participated in the PACE meeting. The key points of their joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company conducted an economic analysis, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (48.2 years)
Population	The submitting company proposed a more limited positioning than the licensed indication for zilucoplan, as follows: Adult patients with refractory anti-AChR antibody positive gMG, as an add-on to standard therapy, if: • the disease has not responded adequately to CSs and at least two other treatments including NSISTs and rituximab (for example: one NSIST and rituximab or two NSISTs), or these options are contraindicated or not tolerated; and • the disease is uncontrolled, as defined by an MG-ADL score of ≥6 or a QMG score of ≥12; and • patients are being considered for, or treated with, maintenance IVIg or PLEX.
Comparators	The main comparator considered by the submitting company was Ig as an add-on to standard therapy, consisting of 15% SCIg and 85% IVIg. PLEX as an add-on to standard therapy was considered as a secondary comparator, given that it is not commonly used in Scotland.
Model description	A Markov model was used, with health states corresponding to uncontrolled disease, response to treatment (subdivided into continued, stable and loss of response), acute exacerbation, myasthenic crisis and death. All patients were assumed to start in the uncontrolled disease health state, potentially moving to a response health state at the time of response assessment (assumed to be 3 weeks from baseline). Patients in the response health states were assumed to remain in the same health state until they experienced acute exacerbation, myasthenic crisis, or death. From the exacerbation and myasthenic crisis states, patients were assumed to discontinue treatment and return to the uncontrolled disease health state, and treatment with standard therapy (CSs or NSISTs). A simplified scenario analysis was also conducted which included the impact of subsequent treatments. MG-ADL score was tracked for each health state over time, largely to facilitate assignment of utility values. A cycle length of two weeks was used, with no half-cycle correction, due to the short cycle length. AEs were not included in the model, due to the low incidence of AEs in the RAISE study.[6]
Clinical data	The probabilities of response were informed by the submitting company's bivariate NMA (including both RCTs and non-RCTs). The proportion of patients experiencing continued/stable/loss of response were informed either by the RAISE-XT study or input from Scottish clinical experts. Transition probabilities to the acute exacerbation, myasthenic crisis and death health states were informed by RWE and RCT data from the literature.[13, 14] Changes in MG-ADL score over time were estimated based on data from the RAISE study.[6]
Extrapolation	Transition probabilities (with the exception of mortality) were assumed to be constant over time. After initial changes to MG-ADL upon starting treatment, in the long-term, MG-ADL was assumed to be constant over time for each health state.
Quality of life	Health benefits were measured in QALYs. Utility values were obtained from HRQoL data collected in the RAISE study[9], by fitting a linear mixed model for repeated measures which included a covariate for MG-ADL score; utility values were assigned to health states on the basis of the associated MG-ADL score for each model cycle. A disutility was also applied for

	patients receiving treatment requiring IV administration; the input value used was derived from a vignette-based utility study of haemophilia A.[15]
Costs and resource use	The economic model included treatment acquisition and administration costs, and resource use for each health state (including rescue therapy in the acute exacerbation and myasthenic crisis health states, visits to healthcare professionals, and management of steroid use). Frequency of resource use was informed by an RWE study.[16] One-off costs were applied on death to account for end-of-life care and applied at baseline for patients treated with zilucoplan to account for the requirement for a meningococcal vaccine.
PAS/contract price	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A contract price is in place for IVIg and this was included in the results used for decision-making.

Abbreviations: AChR= acetylchoinereceptor; AE=adverse event; CS=corticosteroid; gMG=generalised myasthenia gravis; HRQoL= health-related quality of life; Ig=immunoglobulin; IV=intravenous; IVIg=intravenous immunoglobulin; MG-ADL=Myasthenia Gravis Activities of Daily Living; NSIST=non-steroidal immunosuppressant therapy; PLEX=plasma exchange; QALY=quality-adjusted life year; QMG=; RCT=randomised controlled trial; RWE=real-world evidence; SCIg=subcutaneous immunoglobulin.

6.2. Results

This resubmission has been assessed under the fast-track resubmission process. The base case results are presented in Table 6.2. SMC would wish to present the cost-effectiveness results that were used for decision-making. However, SMC is unable to publish these results due to commercial in confidence concerns.

Table 6.2 Base Case Results

	Total costs (£)	**Total QALYs**	**Incr. costs (£)**	**LYs**	**Incr. QALYs**	**ICER (£/QALY)**
Zilucoplan	CIC	9.746				
IVIg/SCIg	CIC	9.633	CIC	0.000	0.113	CIC
PLEX	CIC	9.699	CIC	0.000	0.048	CIC

Abbreviations: CIC = commercial in confidence; ICER=incremental cost-effectiveness ratio; IVIg=intravenous immunoglobulin; LYs, life years; PLEX=plasma exchange; QALYs=quality-adjusted life years; SCIg=subcutaneous immunoglobulin.

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in Tables 6.3 and 6.4.

Table 6.3 Scenario analysis results (zilucoplan vs IVIg/SCIg)

	Parameter	**Base case**	**Scenario**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£/QALY)**
	Base case			CIC	0.113	CIC
1	Exacerbation rates	Abuzinadah *et al.* 2021	Ting *et al.* 2025	CIC	0.115	CIC
2	Baseline characteristics	Refractory gMG population	Overall gMG population	CIC	0.113	CIC
3	Perspective	Scottish NHS and social services	Scottish NHS, social services	CIC	0.184	CIC

			and societal perspective			
4	Disutilities for corticosteroid use	Excluded	Included	CIC	0.143	CIC
5	Proportion of responders	Bivariate NMA	Two-stage baseline risk-adjusted NMA	CIC	0.145	CIC
6	Subsequent treatments	Excluded	Included	CIC	0.112	CIC
7	Proportion of Ig patients receiving SCIg	15%	0.845%	CIC	0.113	CIC
8	Patients' weight distribution	RAISE trial	UK RWE (Adelphi Real World Disease Specific Programme™)	CIC	0.113	CIC
9	IVIg/SCIg dose	1 g/kg	1.5 g/kg	CIC	0.113	CIC
10	Time to response assessment	3 weeks for all treatments	12 weeks for zilucoplan, 6 weeks for IVIg/SCIg	CIC	0.144	CIC
11	CS costs in the continuous response health state for zilucoplan	Excluded	Included	CIC	0.113	CIC
12	Discontinuation informed by RAISE-XT in addition to discontinuation due to clinical events	Included	Excluded	CIC	0.113	CIC
13	Cost-minimisation approach	Not used	Used	CIC	0.000	CIC
14	Proportion of responders	Point estimate of bivariate NMA	Lower bound of 95% CrI	CIC	0.084	CIC
15	Proportion of responders	Point estimate of bivariate NMA	Upper bound of 95% CrI	CIC	0.146	CIC
16	Price for IVIg/SCIg	List price	National framework contract price	CIC	0.113	CIC

Abbreviations: CIC=commercial in confidence; gMG=generalised myasthenia gravis; ICER = incremental cost-effectiveness ratio; IVIg=intravenous immunoglobulin; MG-ADL=Myasthenia Gravis Activities of Daily Living; NMA=network meta-analysis; PLEX=plasma exchange; QALY=quality-adjusted life year; RWE=real-world evidence; SCIg=subcutaneous immunoglobulin.

Table 6.4 Scenario analysis results (zilucoplan vs PLEX)

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case			CIC	0.048	CIC
1	Exacerbation rates	Abuzinadah *et al.* 2025	Ting *et al.* 2025	CIC	0.048	CIC
2	Baseline characteristics	Refractory gMG population	Overall gMG population	CIC	0.036	CIC
3	Perspective	Scottish NHS and social services	Scottish NHS, social services and societal perspective	CIC	0.096	CIC
4	Disutilities for corticosteroid use	Excluded	Included	CIC	0.046	CIC
5	Proportion of responders	Bivariate NMA	Two-stage baseline risk-adjusted NMA	CIC	0.013	CIC
6	Subsequent treatments	Excluded	Included	CIC	0.054	CIC
7	Proportion of Ig patients receiving SCIg	15%	0.845%	CIC	0.048	CIC
8	Patients' weight distribution	RAISE trial	UK RWE (Adelphi Real World Disease Specific Programme™)	CIC	0.048	CIC
9	IVIg/SCIg dose	1 g/kg	1.5 g/kg	CIC	0.048	CIC
10	Time to response assessment	3 weeks for all treatments	12 weeks for zilucoplan, 6 weeks for IVIg/SCIg	CIC	0.066	CIC
11	CS costs in the continuous response health state for zilucoplan	Excluded	Included	CIC	0.048	CIC
12	Discontinuation informed by RAISE-XT in addition to discontinuation due to clinical events	Included	Excluded	CIC	0.048	CIC
13	Cost-minimisation approach	Not used	Used	CIC	0.000	CIC
14	Proportion of responders	Point estimate of bivariate NMA	Lower bound of 95% CrI	CIC	0.094	CIC
15	Proportion of responders	Point estimate of bivariate NMA	Upper bound of 95% CrI	CIC	0.012	CIC

16	Price for IVIg/SCIg	List price	National framework contract price	CIC	CIC	CIC

Abbreviations: CIC=commercial in confidence; gMG=generalised myasthenia gravis; ICER = incremental cost-effectiveness ratio; IVIg=intravenous immunoglobulin; MG-ADL=Myasthenia Gravis Activities of Daily Living; NMA=network meta-analysis; PLEX=plasma exchange; QALY=quality-adjusted life year; RWE=real-world evidence; SCIg=subcutaneous immunoglobulin.

6.4. Key strengths

The strengths of the submitting company's analysis are as follows:

- The model structure used by the company was broadly appropriate.
- The submitting company consistently used evidence from the key studies for zilucoplan, RAISE and RAISE-XT, where possible.
- The submitting company's approach to measuring utility values appeared to be in line with the existing literature.
- The submitting company used appropriate sources to parametrise costs and resource use in the economic model.

6.5. Key uncertainties

The submitting company's analysis was subject to several uncertainties, as follows:

- Costs and benefits of subsequent treatments were not included by the submitting company in their base case analysis; a scenario analysis was presented in which costs and benefits of subsequent treatment were modelled, but the approach taken was dependent on a strong assumption of a 'steady state' of patients receiving subsequent treatment, and the input parameters lacked face validity. Accurate inclusion of subsequent treatment in the model would be expected to increase costs and QALYs in both arms, but the overall impact on incremental results is unclear.
- Clinical inputs were derived from the submitting company's NMAs; these were conducted in a patient population which does not align with the proposed positioning of zilucoplan (in particular, the population is not limited to treatment-refractory patients). This is an unavoidable drawback in the submitting company's approach due to lack of available data in the population of interest. However, this may have a limited impact on results in the economic analysis; since zilucoplan has a novel mechanism of action, there is no specific reason why patients in a treatment-refractory population should respond differently to the full patient population.
- The probability of response inputs were derived from the bivariate NMA in the submitting company's base case; however, the two-stage NMA may be a more appropriate source, given that this corrected for differences in baseline response. The scenario analysis performed by the submitting company suggests that using the two-stage NMA and comparing to IVIg/SCIg results in a reduction in incremental costs for zilucoplan, and an increase in incremental QALYs. However, the overall uncertainty in the results is increased, given the wider credible intervals for the two-stage NMA

compared to the bivariate NMA. The impact on other comparators is unclear. The submitting company also included a cost-minimisation analysis with an assumption of equal efficacy between treatment arms.

- Several key clinical inputs were informed only by clinical expert opinion rather than from existing data or studies. A structured framework was not used to elicit expert opinions. It is unclear whether this would bias the economic results in a particular direction, but this adds to the overall uncertainty of the economic analysis.
- The model inputs for the disutility for steroid use and IV administrations, and the annual cost of managing corticosteroid use, were parametrised based on data for patients with other conditions, due to the lack of availability of gMG-specific alternatives. It is unclear whether this would bias the economic results in a particular direction, but this adds to the overall uncertainty of the economic analysis.
- The cost of IVIg in NHS practice is lower than the price used in the economic model due to the existence of a national framework agreement for this medicine. Using the national framework contract price has a substantial upward impact on the cost-effectiveness results.

7. Conclusion

The Committee considered the benefits of zilucoplan in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as zilucoplan is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted zilucoplan for restricted use in NHSScotland.

8. Guidelines and Protocols

The Association of British Neurologists (ABN) published myasthenia gravis guidelines in 2015. This guidance was subsequently updated in 2025.[5, 17]

International consensus guidance for the management of myasthenia gravis was published in 2016 by the American Academy of Neurology. This guidance was subsequently updated in 2020.[18, 19]

9. Additional Information

9.1. Product availability date

April 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year
zilucoplan	**Administered as a SC injection once daily at the following recommended doses: 16.6 mg (<56 kg body weight); 23 mg (>56 to <77 kg); 32.4 mg (≥77 kg).**	**<56 kg = £189,549** **≥56 to <77 kg = £262,630** **≥77 kg = £369,964**

Costs from BNF online on 03 October 2025. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 161 patients eligible for treatment with zilucoplan in year 1 and 170 patients in year 3. The estimated uptake was 2% in year 1 and 11% in year 3 with a discontinuation rate of 9% and 18% applied in year 1 and year 3 respectively. This resulted in four patients estimated to receive treatment in year 1 rising to 15 patients in year 3.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 22 May 2026.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.