NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Ravulizumab for treating 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 ravulizumab 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: September 2023

Note that this document is not NICE's final guidance on ravulizumab. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using ravulizumab in the NHS in England.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 October 2023
- Second evaluation committee meeting: 16 November 2023
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Ravulizumab 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 ravulizumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Standard treatment for generalised myasthenia gravis in adults who test positive for anti-acetylcholine receptor antibodies includes surgery, acetylcholinesterase inhibitors or immunosuppressants. Ravulizumab would be used as an add-on to standard treatment.

Clinical trial evidence suggests that ravulizumab plus standard treatment improves symptoms and people's ability to do their normal activities compared with standard treatment alone. But it is uncertain if the people in the trial reflect the people who would have ravulizumab in the NHS.

There are also uncertainties in the economic model that make the cost-effectiveness estimates for ravulizumab uncertain. These estimates are above what NICE considers an acceptable use of NHS resources. So, ravulizumab is not recommended.

2 Information about ravulizumab

Marketing authorisation indication

2.1 Ravulizumab (Ultomiris, Alexion) is indicated as 'an add-on to standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody-positive'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for ravulizumab.

Price

2.3 The list price for ravulizumab is £4,533 for the 3 ml (100 mg/ml) vial and £16,621 for the 11 ml (100 mg/ml) vial (excluding VAT; BNF online accessed September 2023).

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

3 Committee discussion

The evaluation committee considered evidence submitted by Alexion, 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 75% of people, it will affect other muscle groups and become generalised myasthenia gravis (gMG). Around 90% of people with gMG have anti-acetylcholine receptor (AChR) antibodies. Symptoms of gMG include difficulties with swallowing, vision, speech, breathing, mobility, and fatigue. The patient experts explained that symptoms of gMG can vary and that their impact can also

change from day to day. They explained the condition can have substantial physical, emotional, and financial impacts on the person with gMG, as well as their carers. Around 15% to 30% of people with gMG experience a myasthenic crisis at least once, where the muscles that control breathing are affected. This needs intensive care support and is the main cause of MG-related deaths. There is currently no cure for gMG. The clinical expert explained that finding treatments that control symptoms can be challenging and can take a considerable length of time. The clinical expert added that sometimes it can take up to 18 months to determine whether the condition is responding to a treatment. The patient experts stated that during this time when symptoms are not well controlled, support is needed from family, friends and employers. The patient experts explained that there is a high unmet need for effective treatments. They noted that current treatments for gMG are associated with side effects that need managing. They explained that many people with gMG need corticosteroids, but finding a dose that manages symptoms while minimising the impact of side effects is challenging. They also said that strict treatment schedules can impact daily life and highlighted the difficulties in managing these and side effects of multiple treatments. The committee concluded that gMG is a debilitating condition with a high treatment burden.

Clinical management

Treatment options

3.2 gMG is a chronic condition and most people need lifelong treatment. There is no single universally accepted treatment pathway for gMG and the committee were aware that the Association of British Neurologists (ABN; 2015) guidelines were being updated at the time of the appraisal. The ABN (2015) guidelines recommend that people are first offered pyridostigmine at the lowest effective dose and that surgery to remove the thymus gland can be considered for people under 45 years. If symptoms continue, people should be offered prednisolone. The clinical expert

explained that corticosteroids like prednisolone are associated with notable side effects and that they aim to use the lowest effective doses to minimise these. The ABN guidelines recommend that people are offered non-steroidal immunosuppressive therapy (NSIST) such as azathioprine if remission is not achieved on corticosteroids alone. If their condition does not respond to immunosuppressants or they experience notable side effects on increasing corticosteroid doses, expert advice should be sought on the use of plasma exchange or intravenous immunoglobulin (IVIg). The NHS England commissioning criteria policy for the use of therapeutic immunoglobulin recommends IVIg should be used:

- when urgent inpatient treatment is needed and plasma exchange is not available
- in rare circumstances as a maintenance treatment when all standard treatments have failed and the person is having treatment in a specialist neuromuscular service.

The NHS England Clinical Commissioning Policy statement on rituximab biosimilars recommends that rituximab is used in later lines of therapy or for 'explosive' onset MG that is unresponsive to conventional rescue treatments. The clinical expert and patient experts explained that existing treatments are not only associated with notable side effects but can be slow to take effect. The committee concluded that people with gMG and clinicians would welcome an effective and fast-acting treatment option, particularly when rapid effect is needed or the condition does not respond to standard therapy.

Proposed positioning and population

3.3 Ravulizumab has a marketing authorisation as an add-on to standard therapy for adults with gMG who test positive for AChR antibodies. The company positioned ravulizumab, more specifically, as a treatment for AChR antibody-positive gMG in adults after at least 1 immunosuppressive therapy. The clinical expert considered that ravulizumab could be

positioned at various points in the clinical pathway. They stated that it could be used in people with substantial symptoms despite optimal standard treatment including a standard NSIST such as azathioprine, described as a 'refractory' population. They also explained that ravulizumab could be used to treat severe, explosive onset gMG. Because ravulizumab is fast-acting, it could be an option while waiting for other oral agents to take effect, potentially reducing the corticosteroid dose needed. The committee considered that the population with explosive onset gMG may not be included within the licensed indication, since ravulizumab is licensed as an add-on to standard therapy and people with explosive onset gMG may not be having standard therapy. The clinical expert highlighted that ravulizumab could be particularly useful in the small cohort (5% to 10% of everyone with gMG) of people who depend on 'rescue treatments' such as IVIg or plasma exchange (PLEX; see section 3.2), for chronic symptom control. The committee considered the company's proposed positioning of ravulizumab, as a treatment for AChR antibody-positive gMG in adults after at least 1 immunosuppressive therapy. It noted that this proposed positioning was broader than that suggested by the clinical expert. The committee also considered that the company's positioning of ravulizumab was not clear, especially the positioning relative to rituximab, IVIg or PLEX. The committee noted that the company used efficacy data from CHAMPION-MG in its model (see section 3.7) and that the inclusion criteria did not specify previous immunosuppressive treatment. So, the committee considered that the inclusion criteria for CHAMPION-MG may not reflect the population that would most likely be offered ravulizumab in NHS clinical practice, as suggested by the clinical expert. The committee highlighted that the clinical and cost effectiveness of ravulizumab would change for different populations. It concluded that it would like further clarification from the company on the proposed positioning of ravulizumab in the treatment pathway, including its positioning relative to rituximab, IVIg and PLEX. It would also like further clarification about whether this

positioning reflects the populations that the clinical expert said ravulizumab would most likely be offered to in the NHS.

Comparators

3.4 The company positioned ravulizumab as a treatment for AChR antibody-positive gMG in adults after at least 1 immunosuppressive therapy. The EAG noted that the comparator of standard care (SoC) in the company's submission comprised a 'basket' of relevant steroids and NSISTs but not rituximab. The company did not believe rituximab was an appropriate comparator because:

- there is limited robust data to support use of rituximab for treating AChR antibody-positive gMG and most evidence is for muscle specific tyrosine kinase (MuSK) antibody-positive gMG
- rituximab can interact with COVID-19 symptoms (the EAG noted that the company did not clarify the specific meaning of this) so it is generally reserved for severe gMG
- rituximab is used in later lines of therapy as a last resort for people who have had all other treatment options as per the NHS England Clinical Commissioning Policy statement on rituximab biosimilars
- there is a lack of robust studies on rituximab in 'refractory' gMG so there is no appropriate data for a comparison of ravulizumab with rituximab.

The EAG's clinical advisers suggested that rituximab is used in clinical practice as a component of standard care for AChR antibody-positive gMG. The EAG's clinical advisers said that they were not overly concerned about limitations placed on rituximab by COVID-19 because rituximab can be offered to people who have had the COVID-19 vaccination. In response to the company stating that rituximab is used in later lines of therapy, the EAG noted that people with 'refractory' gMG are covered by the licensed indication. It added that the company does not state whether ravulizumab would be used before, instead of, or after,

rituximab therapy. The EAG agreed that it is unlikely there is adequately robust clinical efficacy evidence to enable an indirect treatment comparison (ITC) between ravulizumab and rituximab. The clinical expert stated that rituximab takes longer to take effect than ravulizumab. They added that in their practice, rituximab has limited use and disappointing efficacy in AChR antibody-positive gMG, so they do not consider it to be a comparator. The committee considered that, although rituximab may have limited use and efficacy in AChR antibody-positive gMG, it is still a treatment option and so is potentially a comparator. The committee recalled the uncertainty in the positioning of ravulizumab in the treatment pathway, particularly relative to rituximab, IVIg and PLEX (see section 3.3). Depending on the positioning of ravulizumab, the committee would like to see cost-effectiveness analyses of ravulizumab compared with rituximab. The committee also considered that ravulizumab use may affect the proportion of people having subsequent treatments such as IVIg and PLEX. It concluded that, depending on the positioning of ravulizumab, it may be appropriate to include subsequent treatment costs in the cost-effectiveness analysis. Also, depending on ravulizumab's positioning, rituximab, IVIg and PLEX may be potentially relevant comparators.

Clinical effectiveness

CHAMPION-MG trial and CHAMPION-MG open-label extension

3.5 The clinical evidence for ravulizumab came from CHAMPION-MG and the CHAMPION-MG open-label extension (OLE) study. CHAMPION-MG was a phase 3, double-blind, international randomised controlled trial. It compared the efficacy and safety of ravulizumab as an add-on therapy to SoC compared with placebo plus SoC, over a 26-week period, in people with anti-AChR antibody-positive gMG (n=175). It recruited adults with a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of 6 points or more, who had not previously had complement inhibitor treatment. The primary outcome was change from baseline MG-ADL total score at week 26, where a reduction in the score (a negative change)

reflects an improvement in symptoms. At week 26, the mean (least square) change from baseline in MG-ADL total score in the ravulizumab arm was -3.1, compared with -1.4 in the placebo arm ($p<0.001$). In the company's economic model, a 'response' was defined as a reduction in the MG-ADL total score of at least 3 points. At week 26, 56.7% (adjusted based on generalised linear mixed model) of people in the ravulizumab arm had a reduction in the MG-ADL total score of at least 3 points, compared with 34.1% (adjusted) in the placebo arm (p-value not reported). CHAMPION-MG OLE is an ongoing single-arm study to assess the safety and efficacy of ravulizumab up to 2 years after the end of the randomised controlled period of CHAMPION-MG. The latest data cut provides results up to 60 weeks from the time of randomisation. For people assigned to ravulizumab in CHAMPION-MG, the improvement in MG-ADL total score was sustained from week 26 to week 60 in the OLE study. For people assigned to placebo in CHAMPION-MG, there was an improvement in the MG-ADL total score from week 26 to week 60 in the OLE study. The exact change in total MG-ADL scores in the OLE study are considered confidential by the company and cannot be reported here. The committee concluded that ravulizumab as an add-on to SoC is more effective at improving MG-ADL score than SoC alone.

Including the REGAIN trial of eculizumab

3.6 To provide a larger dataset and a longer follow up to predict clinical outcomes for ravulizumab, the company included data from another complement inhibitor, eculizumab. In addition to data from CHAMPION-MG, the company used data from REGAIN, a randomised controlled trial comparing eculizumab with placebo in adults with AChR antibody-positive gMG. It also used data from the REGAIN OLE study, which provided outcomes data for up to 4 years. Ravulizumab and eculizumab have the same mechanism of action and over 99% homology (similarity of structure). So, the company assumes that these therapies have similar efficacy and safety. To show similar clinical effectiveness, the company did 3 types of ITC of eculizumab compared with ravulizumab using

CHAMPION-MG and REGAIN, with the placebo (SoC) arm as the common comparator. The 3 types of ITC were: unadjusted analysis, matching-adjusted indirect comparison and inverse probability weighting. Overall, the ITC results lacked statistical significance, which the company interpreted as indicating similar efficacy between eculizumab and ravulizumab. The exact results of the ITC are considered confidential and cannot be reported here. The EAG stated that confidence in the ITC results is undermined by missing prognostic factors and lack of sensitivity analysis. It also highlighted that there are 2 assumptions being made by the company: that eculizumab and ravulizumab have comparable clinical effectiveness in the short term; and that short-term comparable clinical effectiveness of these therapies can predict long-term clinical effectiveness of ravulizumab. The company's ITC only informs the first of these assumptions. Because the ITC was limited to a relatively short-term comparison (26 weeks) and because of the methodological limitations, the EAG considered the results highly uncertain. The EAG was aware that previous NICE appraisals in other indications considered eculizumab to have similar effectiveness as ravulizumab. But the EAG's clinical experts considered that these appraisals have uncertain relevance to gMG because they were for different conditions. The EAG did not believe there was convincing evidence of similar clinical effectiveness between these treatments. The committee considered that long-term outcomes of ravulizumab were uncertain. Because of methodological limitations highlighted by the EAG, the committee also considered that the results of the ITC were uncertain. The committee also noted that the ravulizumab dosage is based on body weight (see section 2.2) but in REGAIN there was a fixed eculizumab dose for everyone. The committee considered this an added uncertainty. It concluded that the assumption of similar efficacy between ravulizumab and eculizumab was highly uncertain. It also concluded that the uncertainty related to long-term outcomes of ravulizumab would only be reduced by availability of longer-term data. It

invites the company to provide further data, if available, from later data cuts of CHAMPION-MG OLE.

Economic model

Company's modelling approach

3.7 The company presented a 3-state cohort-based Markov model. The model consisted of 2 alive health states differentiated by treatment status ('on ravulizumab' and 'on SoC'), and a death state. The 2 alive health states were subdivided into 7 substates defined by change in MG-ADL score from baseline in the CHAMPION-MG RCT (below 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, 7 to 8, 8 and above), to reflect the differing levels of patient benefit in each treatment arm. In the ravulizumab arm, except for people who stop treatment, the model assumes no transition between the substates: people stay in the same substate after their initial MG-ADL score change. People in the ravulizumab arm who stop treatment transfer to SoC and remain there until death. In the SoC arm, the company assumed that people stay in the same MG-ADL change substate in the first year of the model before returning to baseline (to account for the placebo effect, see section 3.9). People in the SoC arm remain on standard treatment with no treatment stopping until death. The model also includes 2 gMG-associated clinical events: exacerbations and crises. The committee concluded that the company's model structure was appropriate for decision making.

Long-term treatment effects

3.8 The company stated that in clinical practice, assessment of response to ravulizumab would take place after about 2 treatment cycles at 16 weeks. But assessment data was not collected in CHAMPION-MG at 16 weeks, so data from the 18-week assessment was used in the economic model to estimate response to ravulizumab. In the economic model, people in the ravulizumab arm with a reduction of less than 3 points in MG-ADL total score at 16 weeks (based on 18-week CHAMPION-MG data) were

assumed to stop treatment. After changes in MG-ADL based on 18-week data, people in the ravulizumab arm were assumed to remain in the same MG-ADL substate for the remaining duration of treatment. In the SoC arm, the company used 26-week data (rather than 18-week data) to assign people to MG-ADL substates. It stated that this difference in timepoints was because of the difference in the 'speed of onset' for effects between ravulizumab and SoC. The EAG agreed that using 18-week data measured in CHAMPION-MG is a reasonable proxy for the ravulizumab treatment effect at 16 weeks. But for the long-term treatment effect (assignment to long-term MG-ADL substates), it considered that it would be more appropriate to use the measure of MG-ADL change to 26 weeks for ravulizumab. This would match the timepoint for the SoC arm and make full use of all CHAMPION-MG randomised data to project long-term outcomes. The committee agreed with the EAG that it would be more appropriate to use the measure of MG-ADL change to 26 weeks for ravulizumab to model the long-term treatment effect. It also noted that 60-week data from the CHAMPION-MG OLE study was available and could be used in the model to reduce the uncertainty about the long-term treatment effect of ravulizumab. The company stated that the difference between the 26-week and 60-week data was not substantial but there was a higher proportion of response at week 60. The committee concluded that it prefers the scenario that uses the 18-week data to estimate response to ravulizumab, combined with 26-week data to model the long-term treatment effect of ravulizumab. It would also like to see a scenario that incorporates the 60-week data to model the long-term treatment effect of ravulizumab. The committee also concluded that response would be assessed at 16 weeks in clinical practice, and that it would be reasonable to stop treatment if people had less than a 3-point reduction in MG-ADL total score. It noted that because the modelling was based on this, any positive recommendation for ravulizumab would also need to reflect this stopping rule.

Placebo effect

3.9 In the SoC arm of CHAMPION-MG, there was improvement from baseline to week 26 in the total MG-ADL score (see section 3.5). The company attributed this to a placebo effect, noting that the improvement in MG-ADL score happened despite people remaining on a stable dose of immunosuppressive therapy that was in line with their treatment before entering the trial. Because the trial permitted continuing standard care, the company suggested that the improvement in MG-ADL score may represent part of a natural fluctuation. Because only 26 weeks of follow up were reported, it believed it plausible that the MG-ADL scores would have stabilised and the placebo effect would not persist long term. This view was supported by the 2 clinical experts at an advisory board conducted by the company. The company believed that maintaining this treatment effect long term in the economic model would result in a substantial underestimation of ravulizumab's relative effectiveness compared with SoC, and in turn its cost effectiveness. So in its base case, in the SoC arm, the company assumed that people experience the treatment effect seen in the trial for the first year of the model before returning to the baseline MG-ADL score. The EAG noted that the company's assumption, that the placebo effect could represent a natural fluctuation in outcomes and would not persist in the long term, is speculative and based solely on limited clinical expert opinion. The EAG incorporated the company's modelling assumption (MG-ADL assumed to return to baseline at 1 year in the SoC arm) in its base case but noted that this was uncertain. It explored alternative scenarios: MG-ADL returning to baseline at 6 months, MG-ADL returning to baseline at 9 months and no loss of placebo effect (no return to baseline). The scenarios where MG-ADL returned to baseline at 6 or 9 months resulted in a small decrease in the incremental cost-effectiveness ratio (ICER). The 'no loss of placebo effect' scenario resulted in a large increase in the ICER. The committee considered that data beyond 26 weeks for the SoC arm was not available from CHAMPION-MG, CHAMPION-MG OLE, or real-world data from a comparable cohort. So there was no empirical basis for assessing how

much of the improvement in the SoC arm was because of regression to the mean (a tendency for extreme values to move closer to the mean when measures are repeated over time), a 'trial' effect (benefit from being in the trial that would apply to both arms, and not in routine practice) or a 'true placebo' effect (benefit from the expectation that treatment may lead to improvement, which would apply to both arms, and may apply in practice). It noted that it is likely that a mixture of the 3 mechanisms would usually apply to different degrees for different populations and trial procedures. But it also noted that the purpose of blinded, randomised controlled trials is to identify the effects caused by the treatment, as opposed to other mechanisms. So, the committee considered the company's approach of assuming return to MG-ADL baseline at 12 months only in the SoC arm to be biased. This is because it assumes mechanisms that explain changes in the SoC arm do not also exist in the active treatment arm. So, it cannot be said that a placebo effect was in 1 arm and not the other arm. The committee preferred to assume there was no return to MG-ADL baseline in the SoC arm.

Baseline characteristics

3.10 Data from REGAIN for eculizumab was used to inform some modelling aspects including baseline patient characteristics in the company's base case. The EAG noted that there was uncertainty about the relevance of REGAIN (see section 3.6). It preferred to use baseline characteristics of the CHAMPION-MG only population to align the model population with the main clinical data source used in the model. The committee considered the assumption of similar efficacy between ravulizumab and eculizumab highly uncertain (see section 3.6). It noted that the impact on the ICER of using pooled data to inform baseline characteristics in the model compared with using CHAMPION-MG only data was small. It concluded that it preferred to use baseline characteristics of the CHAMPION-MG only population because this aligns with the main clinical data source used in the model.

Time on treatment extrapolations

3.11 The company modelled time on treatment by pooling Kaplan–Meier data from CHAMPION-MG, REGAIN and OLE studies. The company stated that it used pooled data because it offered a larger dataset, and provided longer follow-up data, which reduces the uncertainty of the extrapolations. It also noted that time on treatment of ravulizumab and eculizumab showed a similar trend up to the longest available follow-up point in the CHAMPION-MG OLE (60 weeks). It fitted parametric curves to the Kaplan–Meier data to extrapolate beyond the available data. Based on goodness of fit statistics, visual fit to the observed time on treatment data and the plausibility of long-term predictions, the exponential distribution was selected for the company base case. The EAG noted that while all the parametric models had a good fit to the pooled data up to 2 years, there was a plateau and subsequent spike in stopping treatment between year 3 and 4, which none of the parametric distributions fitted. The company stated that the plateau and spike in stopping treatment after year 3 in the REGAIN OLE may be caused by people exiting the study when eculizumab became commercially available in their country of residence. But the EAG highlighted that if this was the case then the REGAIN OLE data is not reflective of stopping treatment in the UK if ravulizumab were to become available in the NHS. Based on this and the uncertainty associated with the clinical similarity between ravulizumab and eculizumab, the EAG preferred to use CHAMPION-MG only data to model time on treatment. Based on goodness of fit statistics, the EAG also preferred to use the exponential distribution. The committee considered the assumption of similar efficacy between ravulizumab and eculizumab highly uncertain (see section 3.6). It noted that the impact on the ICER of using pooled data to inform time on treatment extrapolations in the model compared with using CHAMPION-MG only data was small. It concluded that it preferred to use CHAMPION-MG only data to model time on treatment. It also noted that this aligns with the main clinical data source

used in the model. It further concluded that the exponential distribution was its preferred distribution.

Incidence of clinical events

3.12 The company fitted a Poisson regression to pooled CHAMPION-MG 60-week data and REGAIN 26-week data to estimate the incidence of acute clinical events (myasthenic exacerbations and crises), for ravulizumab and SoC. The company preferred to use the pooled data rather than CHAMPION-MG only data because this had a larger dataset to fit the regression model. The company base-case Poisson regression model included the independent variables 'treatment' and 'prior clinical event'. The EAG highlighted concerns about the pooled data (see section 3.6) and use of a single 'treatment' variable, grouping the effects of ravulizumab and eculizumab on the incidence of clinical events. It preferred to use the CHAMPION-MG only data because it believed that it has not been shown that ravulizumab and eculizumab have similar effects on clinical event rates. The committee noted that that the impact on the ICER of using pooled data to estimate the incidence of clinical events, compared with using CHAMPION-MG only data, was small. The committee recalled its conclusions on using pooled data to inform certain modelling aspects. It concluded that it preferred to use CHAMPION-MG only data to estimate the incidence of clinical events in the economic model.

Utility values

3.13 The company derived utility values for the economic model using pooled health-related quality of life data for eculizumab, ravulizumab and placebo from CHAMPION-MG and REGAIN. The company's base-case utility regression model included 'MG-ADL score' and 'baseline EQ-5D' as independent variables. The EAG noted that the economic model included options to select 'baseline disease duration' and 'exacerbation or crisis within 3 months' as additional independent variables. But the company did not justify the choice of independent variables for the regression model.

The EAG added that the company did not provide regression statistics to show whether adding or removing alternative independent variables improved the fit of the regression model. The EAG preferred to use the regression model with all 4 independent variables in its base case. The committee noted that the impact on the ICER between the company's and EAG's utility regression models was small. In the absence of regression statistics to show whether adding or removing alternative independent variables improved the fit of the regression model, the committee concluded that it preferred the regression model with all 4 independent variables.

Hospital costs for acute clinical events

3.14 The company's economic model included an assumption on treating a myasthenic crisis. In addition to an intensive care unit (ICU) admission for intubation, the company assumed that a proportion of people will also have an extended ICU stay. The EAG noted that the company's rationale for this assumption was not clear and provided a scenario analysis removing the cost of the extended ICU stay. This resulted in a small increase in the ICER because myasthenic crises are rare events. The cost of a hospital stay requiring intubation in the company's economic model was £4,219, a weighted average for selected non-elective long stay Healthcare Resource Group (HRG) categories from NHS reference costs. The EAG noted that this may be an overestimate and provided a scenario analysis using a lower cost of £870, a weighted average for selected non-elective short stay HRG categories. This resulted in a small to moderate increase in the ICER. In its economic model, the company multiplied the HRG costs for each type of hospital stay (intubation, ICU stay and inpatient care) by an assumed length of stay. The EAG noted that HRG costs already cover an average length of stay per finished consultant episode (FCE) in each category. The company stated that it used this approach because it assumed the length of stay to be longer than the average length of stay per FCE. The EAG did a scenario removing the length of stay multipliers, which resulted in a moderate increase in the

ICER. The committee noted that myasthenic crisis is a potentially life-threatening emergency and so considered that the company's assumption that a proportion of people would have an extended ICU stay was appropriate. But it considered that the company's approach of multiplying HRG costs by the length of stay to be inappropriate because HRG costs already cover an average length of stay per FCE. It also considered the company's estimate of £4,219 for the cost of a hospital stay requiring intubation to be more appropriate than the £870 estimate used in the EAG's scenario analysis. It concluded that if the assumed length of each hospital stay was longer than the average per FCE, the company should have considered alternative methods to account for the relative difference. For example, using a more appropriate multiplier or using 'excess bed day' costs from NHS reference costs.

Cost-effectiveness estimates

3.15 Because of confidential commercial arrangements for ravulizumab and some of the SoC treatments, the exact cost-effectiveness results are confidential and cannot be reported here. In analyses incorporating the company's agreed patient access scheme discount, its base-case ICER was significantly higher than range normally considered a cost-effective use of NHS resources. The EAG's base-case ICER increased this further. The committee noted that neither the company nor the EAG's base cases included all its preferred assumptions. It also noted uncertainty that the population included in the cost-effectiveness model may not reflect the population that would most likely be offered ravulizumab in the NHS if recommended. But, in the modelled population, the committee's preferred ICER was substantially above the range normally considered a cost-effective use of NHS resources.

The committees' preferred assumptions were:

- using the 18-week data to estimate response to ravulizumab, combined with 26-week data to model the long-term treatment effect of

ravulizumab (along with a scenario using the 60-week OLE data to model the long-term treatment effect of ravulizumab; see section 3.8)

- assuming there was no return to MG-ADL baseline in the SoC arm (see section 3.9)
- using the CHAMPION-MG only population to inform the baseline characteristics (see section 3.10)
- using CHAMPION-MG (and CHAMPION-MG OLE) only data to model time on treatment with an exponential distribution (see section 3.11)
- using CHAMPION-MG (and CHAMPION-MG OLE) only data to estimate the incidence of clinical events (see section 3.12)
- using the utility regression model with 4 independent variables: 'MG-ADL score', 'baseline EQ-5D', 'baseline disease duration' and 'exacerbation or crisis within 3 months' (see section 3.13)
- using a more appropriate multiplier or 'excess bed day' costs to account for the relative difference between the assumed length of stay for each type of hospital stay and the average length of stay per FCE in each category (see section 3.14).

Because there was uncertainty about the population that would have ravulizumab in the NHS if it was recommended, the committee would prefer to see analyses that addressed this issue, including:

- clearly identifying and defining the characteristics of the population who would have ravulizumab (see section 3.3)
- clearly defining the proposed positioning of ravulizumab, taking into consideration clinical expert opinion (see section 3.3)
- an assessment of the cost effectiveness of ravulizumab compared with rituximab, IVIg and PLEX, if appropriate (see section 3.4).

Acceptable ICER

3.16 The committee noted that there were several uncaptured benefits in the company's economic analyses (see section 3.18). Because of the uncaptured benefits (see section 3.18), the committee agreed that an

acceptable ICER would be towards the higher end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per quality adjusted life year gained). But the committee considered that if some of these benefits were to be accounted for in subsequent analyses then this may alter the acceptable ICER threshold.

Other factors

Equality

3.17 The committee noted the patient experts' comments that the implications of ravulizumab for people wishing to become pregnant should be considered, and that there are sex and ethnicity-based differences in the age of onset of gMG. The committee noted that issues related to differences in prevalence or incidence of a disease cannot normally be addressed in a technology appraisal recommendation. The committee considered that if ravulizumab was recommended, the decision to use ravulizumab during pregnancy should be made by a patient and their clinician if the clinical benefit outweighs the risks. The committee also noted a clinical expert's comment that there is a need for equity of access to specialist treatment centres for people with gMG. But, the committee noted that access to specialist centres is an implementation issue that cannot be addressed by a NICE technology appraisal recommendation. A clinical expert also highlighted that some people may not wish to have the meningococcal vaccine, which is a prerequisite to starting treatment. The committee considered that any positive recommendation for ravulizumab will state that it is an option, if it is considered an appropriate treatment by patients and their clinicians. No other potential equalities issues were identified.

Uncaptured benefits

3.18 The committee considered benefits of ravulizumab that were not included in the economic model. It noted the quicker onset for ravulizumab compared with SoC. This would allow clinicians to assess whether the

condition was responding, or likely to respond to treatment, after about 2 treatment cycles (16 weeks), allowing change of therapy if there is no response. In contrast, the company stated that with current SoC, people often spend over a year having treatment before response can be accurately assessed. The committee considered that the speed of onset of ravulizumab may provide 'peace of mind' for people with gMG because they can avoid having a long-term treatment that does not benefit them. Patient experts had stated that gMG can have a substantial impact on carers. The committee noted that because ravulizumab improves the symptoms for people with gMG, it may also improve the health-related quality of life of carers. This was not included in the company base case and the committee considered that this was an uncaptured benefit that was relevant but it was not able to quantify. Also, corticosteroids are associated with notable side effects. The committee considered that ravulizumab use may result in reduced corticosteroid use and so reduce corticosteroid-associated complications and side effects. It considered that this may be captured through the quality of life data captured in CHAMPION-MG. But there still may be some uncaptured benefit because of potential reduced costs associated with corticosteroid-associated complications and side effects. The committee considered that this benefit would persist beyond the side effects experienced within the trial period. Another uncaptured benefit in the current analyses was the potential for ravulizumab to reduce the use of subsequent IVIg and PLEX. The committee noted that this may result in substantially reduced costs for the ravulizumab arm if its positioning was consistent with advice from clinical experts that it would be used most in the 'refractory' population. It concluded that these uncaptured benefits did not have a material effect on the decision making at the first committee meeting. This is because they were unlikely to outweigh the committee's concerns about the cost-effectiveness estimates, the degree of uncertainty around the ICER and the uncertainty associated with the positioning of ravulizumab.

Conclusion

3.19 The committee considered that, given its preferred assumptions, the cost-effectiveness estimates for ravulizumab were substantially above the range that NICE normally considers a cost-effective use of NHS resources. But the committee considered the that the modelled population may not reflect the population that would most likely be offered ravulizumab in NHS clinical practice, if recommended. It agreed that further information and analyses were needed to address the uncertainties. The committee concluded that ravulizumab could not be recommended for treating gMG in adults who test positive for AChR antibodies.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Megan John

Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

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