NICE National Institute for Health and Care Excellence

NICE guidance

# Ravulizumab for treating atypical haemolytic uraemic syndrome

Technology appraisal guidance
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# Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

# Contents

# 1 Recommendations

1.1 Ravulizumab is recommended, within its marketing authorisation, as an option for treating atypical haemolytic uraemic syndrome (aHUS) in people weighing 10 kg or more:

- who have not had a complement inhibitor before or
- whose disease has responded to at least 3 months of eculizumab treatment.

It is recommended only if the company provides ravulizumab according to the commercial arrangement (see section 2).

**Why the committee made these recommendations**

Current treatment for aHUS is eculizumab infusions every 2 weeks. People would have ravulizumab infusions every 8 weeks.

Clinical trial evidence suggests that ravulizumab is effective for treating aHUS. But ravulizumab has not been compared directly with eculizumab. The results of indirect comparisons are uncertain, but it is likely that ravulizumab and eculizumab are equally effective because they work in a similar way. Because people have ravulizumab less often than eculizumab it improves quality of life.

Ravulizumab costs less than eculizumab and the cost-effectiveness estimates are within what NICE normally considers an acceptable use of NHS resources. So, ravulizumab is recommended.

# 2 Information about ravulizumab

## Marketing authorisation indication

2.1 Ravulizumab (Ultomiris, Alexion Pharmaceuticals) is indicated for 'the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab'.

## Dosage in the marketing authorisation

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

## Price

2.3 The list price is £4,533 for 300 mg per 3 ml concentrate for solution for infusion vial; £16,621 for 1,100 mg per 11 ml concentrate for solution for infusion vial (excluding VAT; company submission).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes ravulizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

# 3 Committee discussion

The appraisal committee considered evidence submitted by Alexion Pharmaceuticals, a review of this submission by the evidence review group (ERG) and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that 2 issues were resolved during the technical engagement stage, and agreed that:

- treatment with ravulizumab may be stopped if adequate renal response is observed (issue 6, see ERG report table 1)
- the potential future launch of biosimilars of the comparator drug eculizumab (Soliris, Alexion Pharmaceuticals) is not relevant to this appraisal of ravulizumab.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see ERG report pages 10 to 20) and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage.

## New treatment option

### People with atypical haemolytic uraemic syndrome would welcome a new treatment option

3.1 Atypical haemolytic uraemic syndrome (aHUS) is a rare disease that causes blood clots in small blood vessels, which can lead to organ damage. People can have significant kidney impairment, thrombosis, heart failure and brain injury. The patient and clinical experts explained that there is a need for new treatment options for people with aHUS. Current treatment is eculizumab, which people have by intravenous infusion every other week. The patient experts explained that the fortnightly infusions make it difficult for people to work, socialise and join in with family life. People also face the personal, logistical and financial challenges of travelling to have their infusions. People would have ravulizumab by intravenous infusion every 8 weeks, reducing these

challenges greatly compared with eculizumab. The patient experts explained that if ravulizumab were recommended by NICE, people would most likely prefer ravulizumab over eculizumab because of the lower treatment frequency. They noted that longer gaps between treatment reduces the treatment burden, so people who have ravulizumab are likely to have better quality of life than those who have eculizumab. They also noted that they can return to work and arrange holidays. The committee concluded that people would most likely prefer ravulizumab over eculizumab because of the lower treatment frequency and associated positive effect on quality of life.

# Treatment pathway

## Eculizumab is standard first-line therapy for people with aHUS

3.2 In NHS practice, people with aHUS are diagnosed and have treatment through the National aHUS Service, which operates as part of the National Renal Complement Therapeutics Centre. The clinical experts explained that aHUS is diagnosed only after other conditions are ruled out by further tests. Treatment with eculizumab, which NICE's highly specialised technologies guidance on eculizumab recommends for treating aHUS, often starts before these tests are complete. Eculizumab has a short half-life, which is beneficial at the start of treatment because it can be stopped more quickly if an alternative diagnosis is reached. The committee agreed that eculizumab is the standard first-line treatment for people with aHUS.

## Ravulizumab is considered for untreated disease or for people whose disease has responded to at least 3 months of eculizumab treatment

3.3 Ravulizumab has a marketing authorisation for 'the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab'. In line with ravulizumab's marketing authorisation, the company has positioned it as:

- a first-line treatment for people who have not had a complement inhibitor before or
- a second-line or maintenance treatment for people who have had eculizumab for at least 3 months and there has been a disease response.

  The ERG noted that most people would only have ravulizumab as a second-line or maintenance treatment, based on advice from their own clinical experts. This is because of the shorter half-life of eculizumab (see section 3.2). The clinical experts at the committee agreed that most people with suspected aHUS would be offered eculizumab as a first-line treatment, so ravulizumab would be offered as a second-line treatment once the disease had responded to eculizumab. However, the clinical experts also commented that there are some people who could have ravulizumab first line: if there is sufficient evidence that aHUS is the correct diagnosis even ahead of final test results, for example, if there is a family history of aHUS. The committee accepted that ravulizumab could be a treatment option for people who had not had a complement inhibitor before, or for people who had eculizumab for at least 3 months with evidence of a disease response.

# Clinical effectiveness

## Ravulizumab is clinically effective but there is a lack of comparative data

3.4 The company presented evidence for ravulizumab from 2 open-label single-arm studies:

- ALXN1210-aHUS-311, which included 56 adults in 14 countries who had not had eculizumab before

- ALXN1210-aHUS-312, which included 2 groups of young people and children in 8 countries, split into 2 cohorts:
  - cohort 1, which included 18 patients who had not had treatment with eculizumab before
  - cohort 2, which included 10 patients with clinically stable disease after at least 90 days' treatment with eculizumab.

  Both studies consisted of a screening period of up to 7 days, a 26-week initial evaluation period and an extension period of up to 4.5 years. The primary outcome measure for both trials was complete thrombotic microangiopathy (TMA) response. Secondary outcomes included chronic kidney disease (CKD) stage classified as improved, stable (no change), or worsened compared with baseline. 30 adults (54%, 95% confidence interval: 39.6 to 67.5) achieved complete TMA response. 14 children or young people (78%, 95% confidence interval: 52.4 to 93.6) achieved complete TMA response (cohort 1 only). The CKD stage improved in 32 out of 47 adults (68%), and 15 out of 17 children or young people from cohort 1 (88%). CKD stage worsened in 2 out of 47 adults (4%) and in no children or young people in cohort 1. The committee noted that there was no clinical evidence directly comparing ravulizumab with eculizumab because both trials were single-arm studies. It concluded that ravulizumab was clinically effective but agreed that the lack of comparative data made assessing comparative effectiveness (and any consequent cost-effectiveness analyses) very challenging.

## Trial results are generalisable to NHS practice

3.5 The ERG had concerns about the generalisability of the trial results to NHS practice. This was because most patients in the trials had not had eculizumab before ravulizumab. In NHS practice, it is expected that eculizumab will be offered to people suspected of having aHUS until their diagnosis is confirmed. The ERG was also concerned that the trial population did not resemble the UK population of people with aHUS. This was because rates of genetic mutations and autoantibodies characteristic of aHUS were relatively low in the trial population, compared with the rates expected from the scientific literature and clinical practice. The committee noted that clinical practice varies around

the world, and the ERG said it was possible some of the patients in Asia did not have aHUS as per UK diagnostic criteria. The clinical experts agreed that it was possible some patients in the trial did not have aHUS, or that the disease had progressed beyond the usual point of diagnosis in UK practice. They further agreed with the ERG that the low prevalence of genetic mutations and autoantibodies found in people in the trial compared with the known rates of these traits in aHUS suggested some people in the trial did not have the disease. However, the clinical experts explained that the evidence from the clinical trials was sufficiently generalisable to clinical practice. They also confirmed that, in most situations, people would be offered ravulizumab after having treatment with eculizumab, so the issues raised would not be expected in clinical practice. The committee agreed that there was uncertainty in the trial results because of their design, enrolment, and use of genetic testing. But overall, it concluded that the results were generalisable to people seen in NHS practice.

# Indirect treatment comparisons

## The efficacy of ravulizumab compared with eculizumab is based on an uncertain indirect comparison

3.6 There was no trial directly comparing ravulizumab with eculizumab. So the company did indirect treatment comparisons to show the similar effectiveness of the 2 treatments. Data for ravulizumab came from the trials ALXN1210-aHUS-311 and ALXN1210-aHUS-312 (see section 3.4). Data for eculizumab came from 3 other open-label, single-arm trials, aHUS-C08-002, aHUS-C10-003, and aHUS-C10-004. Patients were split into 3 groups: adults who had not had a kidney transplant, adults who had a kidney transplant, and children and young people. The data were weighted according to prognostic criteria measured before treatment, such as dialysis status, estimated glomerular filtration rate and blood pressure to reduce differences between the trial populations. The company compared outcomes across the 3 groups for both treatments. It concluded that there were no statistically significant differences between the 2 treatments; the data did not favour either drug over the other (the results of the comparison are academic in confidence so

cannot be reported here). The ERG disagreed with the company's view and had identified trends in the data that favoured eculizumab over ravulizumab in clinically important outcomes, for example, the number of patients needing dialysis at the end of the trial. To provide more information, the company also discussed data in paroxysmal nocturnal haemoglobinuria (PNH) which directly compared eculizumab with ravulizumab over longer periods of time, and further concluded that the 2 drugs were similarly effective. The ERG did not rely on this dataset as PNH and aHUS are different conditions. The clinical experts said there was unlikely to be much difference between the effectiveness of the 2 drugs, and similar effectiveness was plausible. They also said the small trial size made it difficult to establish statistically significant differences in the effectiveness of the 2 treatments. The committee agreed that the data were uncertain, but accepted it was biologically plausible that ravulizumab and eculizumab may be similarly effective, because of their similar mechanisms of action.

# Adverse events

## Adverse events are likely to be similar for ravulizumab and eculizumab

3.7 The committee noted that deaths had occurred in ravulizumab trial ALXN1210-aHUS-311. There were 3 deaths in the main trial population, 2 from septic shock and 1 from cerebral haemorrhage. One further patient died having previously withdrawn from treatment. The deaths were interpreted by both the company and clinical experts as being a sign that these patients were not representative of people with aHUS seen in UK clinical settings. The committee recalled that some patients in the trials may not have had aHUS, or that the disease had progressed beyond the usual point of diagnosis in UK practice (see section 3.5). The clinical experts stated that they would expect similar adverse event rates for ravulizumab and eculizumab. The committee concluded adverse events are likely to be similar for ravulizumab and eculizumab.

# Economic model

## The company's economic model is suitable for decision making

3.8 The company presented a state transition model with 4 CKD states, 2 states for people needing transplant, and 1 mortality-related state. The model also allowed for some people to stop treatment, and a proportion of those people to relapse and restart treatment. Adults and children and young people were modelled separately, and the results combined. The model was based on the one used in NICE's highly specialised technologies guidance on eculizumab for treating aHUS. The committee concluded that the company's model was suitable for decision making.

# Utility values

## The utility values in the economic model are appropriate

3.9 The company assumed equal clinical effectiveness and quality of life for ravulizumab and eculizumab in their economic model. It also assumed that children, young people and adults with aHUS would all have an equal quality of life. The company did a discrete choice experiment and determined that a quality-of-life utility gain of 0.013 could be added for ravulizumab, because of the reduced frequency of infusions. The committee recalled that this would have a positive effect on quality of life for people with aHUS (see section 3.1). The committee concluded that the quality-of-life utility gain was not a major driver of ravulizumab's cost effectiveness, so accepted the company's utility values in the cost-effectiveness scenario analyses.

# Assumptions in the economic model

## The company's assumption that ravulizumab and eculizumab are equally effective is associated with uncertainty

3.10 In the company's economic model, the long-term efficacy and safety of

ravulizumab was assumed to be equivalent to eculizumab. The ERG highlighted that although this is clinically plausible there is insufficient evidence to support this assumption. The committee agreed and noted this assumption is associated with uncertainty (see section 3.6 and section 3.7). The committee noted that both the company and ERG assumed equal efficacy for ravulizumab and eculizumab in their respective base cases. However, it considered that both had also provided scenario analyses in which different efficacy was assumed based on the results of the indirect treatment comparisons. The committee concluded that although there are biologically plausible reasons why ravulizumab and eculizumab may be similar, there is no direct evidence of this, therefore it would consider assumptions of equal and different efficacy in its decision making.

## There is uncertainty about the long-term safety and efficacy of ravulizumab

3.11 The ERG considered that there was insufficient follow-up data about the long-term safety and efficacy of ravulizumab. It highlighted that, in the company model, long-term efficacy and safety of ravulizumab are assumed to be equivalent to eculizumab (see section 3.6). The ERG considered that although this is clinically plausible, there is no evidence to support this assumption. The ERG was concerned that it was not possible to examine the long-term safety and efficacy of ravulizumab for aHUS. This was because the clinical trial data presented were for initial evaluation periods of 26 weeks in both trials. Trial extension periods were up to 4.5 years, but the data were not available at the time of this appraisal. The committee noted that no long-term data were presented to show that ravulizumab would be safe and effective beyond the duration of the trial. The company accepted this was a limitation of the data and presented long-term data to show ravulizumab remained safe and effective in people with PNH. The ERG did not accept these data were relevant to aHUS. The clinical experts stated they would expect ravulizumab to be effective long term because of the similarities with eculizumab in terms of structure and mechanism of action. The committee agreed the long-term safety and efficacy of ravulizumab remained uncertain, but it was plausible that it would show similar performance to eculizumab. The committee also agreed that it would

take the uncertainty into account in its decision making.

## A time-dependent relapse rate is appropriate for people who stop treatment

3.12 In the company's original base-case model, people who stopped treatment relapsed at a constant rate over time. The ERG argued that this was not accurate, and that rates of relapse vary over time, being highest shortly after treatment withdrawal. The company accepted this and modified the economic model in response to technical engagement to make use of a time-dependent relapse rate obtained from the UK registry of data on people with aHUS. The committee considered that some uncertainty remained because this data source was not the ERG's preferred choice. The ERG suggested obtaining the relapse rate from the global registry of people with aHUS. The ERG stated that using the much larger global dataset also provided more information over time and did not produce results favouring ravulizumab. The ERG stated that only using the UK data increased uncertainty and appeared to favour ravulizumab. The clinical experts said that the relapse rate for people having ravulizumab would be the same as that for eculizumab and did not comment on how the rates change over time. The committee concluded that the company had used an appropriate method and that a time-dependent relapse rate was an appropriate assumption. However, some uncertainty would remain because of the choice of data source.

## Some people may stop and restart treatment multiple times

3.13 The ERG suggested people with aHUS may have multiple treatments in an 'on demand' approach, meaning they may stop treatment then restart if the disease relapses. The ERG noted that results from the ongoing Stopping Eculizumab Treatment Safely (SETS) study may suggest that such an approach could be an appropriate treatment strategy, and that no data had been provided by the company to support this approach. The company stated that this approach does not represent current NHS practice, and that SETS would not examine the scenario in which people stop multiple times. The clinical experts commented that the decision to stop and restart treatment could be made multiple times, but that this would be down to the individual situation of the person with aHUS and

the observed results of them stopping treatment. The clinical experts said this approach may work for some people but not for others. The clinical experts also stated that there were no data to support this approach, and that people may not want to stop and restart treatment multiple times. The committee agreed that this was a possible treatment strategy for some individuals, but that it is not current NHS practice for most people. Therefore, the committee concluded that it would take this possible treatment strategy into account in its decision making.

### It is reasonable to assume that that treatment will stop because of an adequate renal response

3.14 The ERG said that current guidelines suggest treatment for aHUS should be lifelong. But several arguments in the literature propose that people may choose to stop treatment when renal response has reached an adequate level. The ERG expected that this would be supported by the SETS study. The company accepted this argument at technical engagement and updated its economic model to reflect this approach. Stakeholders said that this would be supported by SETS, and that people would want to stop in this case. The clinical experts agreed that although SETS was designed to study eculizumab, its results would apply to ravulizumab in practice. The committee concluded that people may stop treatment with ravulizumab if they achieve an adequate renal response.

## Costs in the economic model

### The costs used in the economic model are appropriate

3.15 The costs used in the company's economic model included drug acquisition, infusion, transplant and maintenance, dialysis, vaccine, stopping, relapse, and costs associated with the different CKD stages. The ERG commented that the costs used by the company were appropriate. It also stated that in its own analyses, the drug acquisition cost was high compared with all other costs, and that all other costs had a very small effect on the overall analysis. So, the key driver of cost effectiveness was the difference in acquisition costs for ravulizumab and eculizumab. The committee concluded that the costs used by the

company in its economic model were appropriate.

### Eculizumab biosimilars may need to be considered in future reviews of ravulizumab

3.16 The ERG highlighted that the patent for eculizumab is set to expire in the next 3 years, so biosimilar eculizumab treatments are likely to enter the market. The committee recalled that the difference in the acquisition costs of ravulizumab and eculizumab were the key drivers of the cost-effectiveness estimates, rather than any difference in the effectiveness of the 2 treatments. So, if biosimilar eculizumab treatments became available with a lower acquisition cost than the currently available eculizumab treatment, this may affect the cost effectiveness of both eculizumab and ravulizumab. However, the committee noted that eculizumab biosimilars are not part of the current pathway of care. The committee agreed that they should not be considered in this appraisal. The committee asked for availability of biosimilars to be factored into future reviews of ravulizumab and its cost effectiveness.

## Cost-effectiveness estimates

### Ravulizumab is a cost-effective use of NHS resources for aHUS

3.17 The committee agreed that its preferred approach to modelling would:

- allow for treatment stopping because of adequate renal response (see section 3.14)
- use a time-dependent relapse rate for people who stop treatment, based on the global registry dataset (see section 3.12)
- allow for 'on demand' treatment with the ability to stop multiple times (see section 3.13)

- include scenarios in which ravulizumab and eculizumab are assumed to be equally effective, and scenarios in which the efficacy of ravulizumab and eculizumab are assumed to be different, because of the uncertainty associated with the results of the indirect comparison (see section 3.6 and section 3.10).

  Using the committee's preferred assumptions and including the revised confidential discount for ravulizumab, ravulizumab was as effective and cost less than eculizumab in both the company's base case and the ERG's preferred base case, when equivalent efficacy was assumed. The exact savings and incremental cost-effectiveness ratio (ICERs) are commercial in confidence and cannot be reported here. When different efficacy was assumed, the cost-effectiveness estimate for ravulizumab was in the south-west quadrant of the cost-effectiveness plane in both the company's and ERG's scenario analyses, meaning it is less effective but costs less than eculizumab. The committee considered that, when an ICER is estimated for a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed. So, the higher the ICER, the more cost effective a treatment is. The committee noted that the south-west quadrant ICERs were high enough to consider ravulizumab a cost-effective use of NHS resources. The committee concluded that ravulizumab can be considered cost effective for treating aHUS.

# Other considerations

## There are no equality issues relevant to the recommendations

3.18 Pregnancy was one of the exclusion criteria for the clinical trials. The summary of product characteristics states that ravulizumab may be offered to pregnant women after an assessment of risks and benefits. The committee acknowledged this and concluded that there were no relevant equality issues.

# Conclusion

## Ravulizumab is recommended

3.19 In the committee's preferred analyses, ravulizumab was considered a cost-effective use of NHS resources compared with eculizumab. Therefore, ravulizumab is recommended as a treatment option for people with aHUS who have not had a complement inhibitor before, or whose disease has responded to at least 3 months of eculizumab treatment.

# 4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has atypical haemolytic uraemic syndrome and the doctor responsible for their care thinks that ravulizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 Appraisal committee members and NICE project team

## Appraisal committee members

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

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

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

## NICE project team

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

**Stephen Norton**
Technical lead

**Nicola Hay**
Technical adviser

**Gavin Kenny**
Project manager

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# Accreditation