NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Ravulizumab for treating paroxysmal nocturnal haemoglobinuria

1 Recommendations

1.1 Ravulizumab is recommended, within its marketing authorisation, as an option for treating paroxysmal nocturnal haemoglobinuria in adults:

- with haemolysis with clinical symptoms suggesting high disease activity, or
- whose disease is clinically stable after having eculizumab for at least 6 months, and
- the company provides it according to the commercial arrangement (see section 2).

Why the committee made these recommendations

Paroxysmal nocturnal haemoglobinuria is currently treated with eculizumab infusions every 2 weeks.

Clinical trial evidence shows that ravulizumab is similarly as effective as eculizumab and is just as safe. Ravulizumab is given less often than eculizumab so there is some benefit on quality of life. Also it may save costs because people need to have it less often.

Ravulizumab is as effective and costs less than eculizumab so it is recommended as an option for treating paroxysmal nocturnal haemoglobinuria.

Issue date: April 2021

2 Information about ravulizumab

Marketing authorisation indication

2.1 Ravulizumab (Ultomiris, Alexion Pharmaceuticals) is indicated for 'the treatment of adult patients with paroxysmal nocturnal haemoglobinuria:

- in patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months'.

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 per 300 mg/3 ml concentrate for solution for infusion vial; £16,621 per 1,100 mg/11 ml concentrate for solution for infusion vial (excluding VAT; company submission).

The company has a commercial arrangement (simple discount). 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:

- the trial populations are generalisable to people seen in clinical practice in England
- the effectiveness of ravulizumab is maintained for as long as the treatment is given.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (ERG report, tables 1.1 to 1.10, pages 10 to 15), and took these into account in its decision making. It discussed the issues, which were outstanding after the technical engagement stage.

New treatment option

People with paroxysmal nocturnal haemoglobinuria would welcome a new treatment option

3.1 The patient and clinical experts explained that there is an unmet need for people with paroxysmal nocturnal haemoglobinuria. Current treatment is eculizumab which must be given 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. They also highlighted the psychological effect of the fortnightly infusions because they are constantly reminded that they have an incurable disease. Also, there is the logistical challenge of arranging infusions, frequent visits from nurses and the frequent canulations can lead to scarring of the veins. Ravulizumab is given by intravenous infusion every 8 weeks. The committee accepted that people with paroxysmal nocturnal haemoglobinuria would welcome a new option that has a longer time between treatments.

Treatment pathway

Eculizumab is the standard therapy for people with paroxysmal nocturnal haemoglobinuria

3.2 In England, people with paroxysmal nocturnal haemoglobinuria are managed by the PNH National Service, consisting of 2 centres and

8 outreach clinics, and their local haematologist through a shared care agreement. The severity of symptoms varies between people and over time, which means that not everyone with paroxysmal nocturnal haemoglobinuria needs treatment. The clinical experts explained that people with high disease activity will be offered eculizumab as laid out by the PNH National Service's indications for treatment with eculizumab. Eculizumab is given by intravenous infusion every 2 weeks and most people choose to get their infusions at home. Most people's disease is well controlled with the licenced dose of 900 mg of eculizumab but some people experience breakthrough haemolysis caused by incomplete C5 inhibition. These people will get a higher dose of eculizumab (1,200 mg) which can also be given more frequently. The committee concluded that eculizumab is the standard treatment for people with paroxysmal nocturnal haemoglobinuria.

People would prefer ravulizumab because of the lower treatment frequency

3.3 The patient experts explained that people prefer ravulizumab instead of eculizumab because it is given every 8 weeks rather than every 2 weeks. They noted that longer treatment breaks reduce the treatment burden and therefore people who have ravulizumab have better health-related quality of life than those who have eculizumab. They also noted that they can return to work and arrange holidays. Results from a patient and carer survey by PNH Support showed that ravulizumab had a positive effect on quality of life. It improved people's independence because of the increased ability to work and had a psychological benefit for individuals and their families because they were able to forget their incurable chronic disease for 8 weeks at a time. In the survey, patients also mentioned that symptom control was as good or better with ravulizumab compared with eculizumab. The clinical experts commented that the reduced frequency of infusions reduces the number of nurse visits which allows them to do other things. They also explained that breakthrough haemolysis from incomplete C5 inhibition is rare with ravulizumab because the

C5 inhibition is more complete compared with eculizumab. Fewer episodes of breakthrough haemolysis reduce the number of hospital admissions and the need for blood transfusions. 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.

Ravulizumab could be considered for people with stable disease who are having eculizumab and people with untreated disease

3.4 Ravulizumab is indicated for treating disease that is stable after 6 months of treatment with eculizumab. The committee understood that clinicians could offer ravulizumab to people who did not experience breakthrough haemolysis and whose disease symptoms did not worsen during 6 months of having eculizumab. Ravulizumab is also indicated for untreated disease with haemolysis and 1 or more symptoms suggestive of high disease activity. High disease activity is not clearly defined, and depends on a number of factors. The committee understood that in the NHS, the criteria for using ravulizumab may be similar to those outlined for eculizumab in the PNH National Service's indication for treatment with eculizumab and that these were reasonable. The criteria for eculizumab are:

- thrombosis related to paroxysmal nocturnal haemoglobinuria
- complications associated with haemolysis:
  - renal failure
  - pulmonary hypertension
- pregnancy (and for at least 3 months post-partum)
- haemolytic symptomatic paroxysmal nocturnal haemoglobinuria.

Clinical effectiveness

Ravulizumab and eculizumab are similarly effective

3.5 The company presented data from 2 non-inferiority phase 3 trials comparing the safety and effectiveness of ravulizumab with eculizumab.

ALXN1210-PNH-301 included adults with paroxysmal nocturnal haemoglobinuria who were complement-inhibitor naive and ALXN1210-PNH-302 included adults with paroxysmal nocturnal haemoglobinuria whose disease was clinically stable following at least 6 months of treatment with eculizumab. Both trials included a 26-week randomised period followed by an extension period of up to 2 years when all patients got ravulizumab. The primary outcomes for ALXN1210-PNH-301 were normalisation of lactate dehydrogenase and achieved transfusion avoidance, and for ALXN1210-PNH-302 was percentage change lactate dehydrogenase from baseline to day 183. The ALXN1210-PNH-301 results showed the odds ratio in lactate dehydrogenase-normalisation rate was 1.19 (95% confidence interval (CI) 0.80 to 1.77) and the difference in achieved transfusion avoidance was 6.8% (95% CI -4.66% to 18.14%). The ALXN1210-PNH-301 results showed the percentage change in lactate dehydrogenase was 9.21% (95% CI -0.42% to 18.8%) and the difference in achieved transfusion avoidance was 5.5% (95% CI -4.3% to 15.7%). The committee noted the point estimates were in favour of ravulizumab but there was no statistically significant difference between ravulizumab and eculizumab for any of the reported clinical outcomes in either trial. It concluded that ravulizumab and eculizumab are similarly effective.

Adverse events with ravulizumab are likely to be similar to those with eculizumab

3.6 ALXN1210-PNH-301 and ALXN1210-PNH-302 showed no difference in adverse events between ravulizumab and eculizumab. The clinical experts explained that from clinical experience over 4.5 years, there were no differences in adverse events between the treatments. The committee acknowledged the European Medicines Agency concluded that the safety profile of ravulizumab appeared to be similar to that of eculizumab. It concluded that adverse events with ravulizumab are likely to be similar to eculizumab.

Trial results are generalisable to clinical practice in England

3.7 In clinical practice some people need an increase in the eculizumab dose after an inadequate disease response or breakthrough haemolysis. This was not allowed in ALXN1210-PNH-301 and ALXN1210-PNH-302. The clinical experts explained that most people do not need a dose increase of eculizumab. They confirmed that clinical outcomes in the trial would have been similar if a dose increase had been permitted. The committee concluded that the results from the trials were generalisable to clinical practice in England.

The company's economic model

The company's model is suitable for decision making

3.8 The company presented a state transition model with 8 breakthrough haemolysis-related health states, 1 mortality-related health state, and a spontaneous-remission health state. The breakthrough haemolysis-related health states were characterised by previous treatment (treatment naive or previously received eculizumab) and breakthrough haemolysis events (no breakthrough haemolysis event, incomplete C5 inhibitor-related breakthrough haemolysis event and complement amplifying condition-related breakthrough haemolysis event). The committee concluded that the company's model was suitable for decision making.

The proportion of people getting a higher dose of eculizumab in the model should be similar to that seen in clinical practice in England

3.9 In the trials only the licenced dose of 900 mg of eculizumab was allowed and a dose increase of eculizumab after breakthrough haemolysis or inadequate response was not permitted. In clinical practice in England, people can get higher doses of eculizumab, typically 1,200 mg, after breakthrough haemolysis and an inadequate disease response. The company included up-dosing in the model using a similar proportion to that seen in clinical practice in England. The ERG cautioned that up-dosing would affect both the costs and the effectiveness of eculizumab

and suggested that up-dosing should be excluded from the model to align with the clinical trial. The committee recalled that up-dosing of eculizumab might not affect clinical outcomes (see section 3.7). It concluded that the proportion of people who get a higher eculizumab dose in the model should be similar to that seen in clinical practice in England.

The utility values in the base-case model should be based on EQ-5D without an additional utility increment

3.10 The committee recalled that people would most likely prefer ravulizumab because of less frequent infusions (see section 3.3). In the trials, health-related quality of life was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C-30) and the results were mapped to EQ-5D-3L. In the model, utilities from a mixed-effects regression model were used. The company included a treatment effect coefficient to capture ravulizumab's quality of life benefit because of reduced treatment frequency. Results favoured ravulizumab but there was no statistically significant difference in health-related quality of life between ravulizumab and eculizumab. The company reasoned that the effect of ravulizumab on treatment burden could not be fully captured in the trial because patients still needed to attend the research site for other trial protocol reasons. So, the company applied an additional utility value of 0.057 for fewer visits for ravulizumab. The ERG preferred using the non-significant treatment effect from the mixed-effects models using EQ-5D data because this already included the reduced infusion frequency. The committee agreed that the utility increment proposed by the company was high when compared with the values from the EQ-5D data. It also agreed that the benefit of lower infusion frequency was captured by the EQ-5D data. It acknowledged that changes in utility values would have no effect on the overall outcome of the cost-effectiveness analysis. It concluded that utility values in the model should be based on EQ-5D data.

Cost-effectiveness estimates

Ravulizumab is a cost-effective use of NHS resources for paroxysmal nocturnal haemoglobinuria

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

- include the sustained effectiveness of ravulizumab (resolved at technical engagement)
- include a dose increase of eculizumab (see section 3.9)
- base utility values on EQ-5D data and not include a utility increment for ravulizumab from the discrete choice experiment (see section 3.10).

Using the committee's preferred assumptions and including the confidential discount for ravulizumab, ravulizumab was more effective and less costly than eculizumab in all scenario analyses presented. Exact results are confidential and cannot be reported here. The committee concluded that ravulizumab when compared with eculizumab is a cost-effective use of NHS resources.

Equality considerations

There are no equality issues relevant to the recommendations

3.12 People under the age of 18 and pregnant people were excluded from the main trials of ravulizumab. Age and pregnancy are protected characteristics which need to be considered. The committee considered issues relating to people included within the marketing authorisation and noted that people under the age of 18 are not included within the marketing authorisation. The committee acknowledged that the use of ravulizumab may be considered for pregnant people after an assessment of the risks and benefits. The committee concluded that there were no relevant equality issues.

Conclusion

Ravulizumab is recommended for routine commissioning

3.13 In the committee's preferred analysis and all the other cost-effectiveness analyses, ravulizumab was more effective and less costly than eculizumab. Therefore, ravulizumab is recommended as a treatment option for paroxysmal nocturnal haemoglobinuria.

4 Implementation

Section 7(6) 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.

4.1 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.

4.2 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 ravulizumab 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 Date for review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the

technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Selby
Chair, appraisal committee
March 2021

6 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.

Verena Wolfram
Technical lead

Sally Doss
Technical adviser

Gavin Kenny
Project manager

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