Cost-effectiveness of ravulizumab (Ultomiris®) for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH), with haemolysis and with clinical symptom(s) indicative of high disease activity; and in patients who are clinically stable after treatment with eculizumab for at least the past six months.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of ravulizumab (Ultomiris®) in adult patients with paroxysmal nocturnal haemoglobinuria (PNH), as per the product licence. Following assessment of the Applicant's submission, the NCPE recommends that ravulizumab (Ultomiris®) be considered for reimbursement provided it does not cost more than existing treatments for PNH. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. The Health Service Executive (HSE) asked the NCPE to carry out a review of the Applicant's (Alexion Pharma UK) Health Technology Assessment of ravulizumab (Ultomiris®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective, including the clinical effectiveness and health-related quality of life benefits, which the new treatment may provide and whether the cost requested is justified.

Following the recommendation from the NCPE, the HSE examines all the relevant evidence. The final decision on reimbursement is made by the HSE. In the case of cancer drugs, the National Cancer Control Programme (NCCP) Technology Review Group also considers the NCPE recommendation.

About the National Centre for Pharmacoeconomics

The NCPE are a multidisciplinary team including clinicians, pharmacists, pharmacologists, information specialists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area. Our aim is to provide impartial advice to help

decision-makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **May 2022**

Summary

In October 2021, Alexion Pharma UK submitted a dossier of clinical, safety and economic evidence on ravulizumab (Ultomiris®) for the treatment of adult patients with PNH as per the product licence. Alexion Pharma UK are seeking reimbursement for ravulizumab in the hospital setting.

PNH is a rare, progressive acquired disease of the blood. It is characterised by uncontrolled terminal complement activation of red blood cells, white blood cells and platelets. In individuals with PNH, the complement system mistakenly destroys blood cells. Transfusion avoidance, haemolysis (based on lactate dehydrogenase normalisation [LDH-N]) and the number of breakthrough haemolysis events are used to estimate clinical response to treatment.

Ravulizumab is a C5 inhibitor. It is a monoclonal antibody that specifically binds to the complement protein C5, preventing the uncontrolled complement activation responsible for triggering PNH disease activity (haemolysis). Ravulizumab was designed by re-engineering eculizumab to achieve a half-life that is four times longer than that of eculizumab. Ravulizumab is formulated as a sterile concentrate for solution for infusion and the recommended dose is based on a patient's bodyweight. The recommended dosing consists of an initial loading dose followed by maintenance dosing once every eight weeks administered via intravenous (IV) infusion. Maintenance dosing starts two weeks after the initial loading dose administration. For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab is administered two weeks after the last eculizumab infusion, and then maintenance doses are administered once every eight weeks, starting two weeks after loading dose administration. Given the chronic nature of PNH, it is anticipated that ravulizumab will be used continuously by patients once initiated, where there is evidence of response.

The current standard of care for adult patients with PNH is eculizumab, another C5 inhibitor treatment. Eculizumab is currently patented but is expected to lose market exclusivity in the next year or two. The dosing regimen for eculizumab consists of a four-week initial phase (600mg once every week by IV infusion) followed by a maintenance phase (900mg administered via IV infusion at week five, followed by 900mg once every two weeks thereafter). The Applicant anticipates that ravulizumab will be used in accordance with the licensed indication as both a first-line therapy and a second-line therapy in patients stable on eculizumab 900mg once every two weeks for at least the past six months. The Applicant suggests that all patients currently stable on eculizumab 900mg once every two weeks could switch to ravulizumab were it to be available; this is supported by clinical opinion. Clinical opinion indicated that patients receiving eculizumab 1,200mg dose once every two weeks would not switch to ravulizumab as there are no data available, currently, to support this decision.

1. Comparative effectiveness of ravulizumab

Clinical evidence is available from two pivotal, phase III, randomised, open-label, active-controlled, multicentre, international, non-inferiority trials. ALXN1210-PNH-301 (n=246) and ALXN1210-PNH-302 (n=195) compared ravulizumab, as per the recommended weight-based dosing regimen, to eculizumab, as per the licensed dosing regimen, in complement inhibitor-naïve and complement inhibitor-experienced patients, respectively. Co-primary endpoints in ALXN1210-PNH-301 included transfusion avoidance and LDH-N and in ALXN1210-PNH-302 the primary endpoint included the percentage change in LDH from baseline. Ravulizumab and eculizumab, respectively, demonstrated improved outcomes at week 26 versus eculizumab; the results were statistically significant and non-inferiority of ravulizumab versus eculizumab was demonstrated (Table 1).

Table 1: Efficacy results for ALXN1210-PNH-301 and ALXN1210-PNH-302

Trial	**ALXN1210-PNH-301**		**ALXN1210-PNH-302**	
Characteristics	Ravulizumab (n=125)	Eculizumab (n=121)	Ravulizumab (n=97)	Eculizumab (n=98)
Mean age at first infusion, years (SD)	44.8 (15.2)	46.2 (16.2)	46.6 (14.4)	48.8 (14.0)
Primary outcomes				
% of patients who avoided a transfusion (95% CI)	73.6 (65.87, 81.33)	66.1 (57.68, 74.55)	87.6 (81.1, 94.2)	82.7 (75.2, 90.2)
Treatment effect (95% CI)	6.8 (-4.66, 18.14)		5.5 (-4.3, 15.7)	

% of patients who achieved LDH-N (95% CI)	53.6 (45.9, 61.2)	49.4 (41.7, 57.0)	66.0**	59.2**
Treatment effect (95% CI)	1.19 (0.80, 1.77)		-	
Percentage change in LDH LS mean (95% CI)	-76.84 (-79.96, -73.73)	-76.02 (-79.20, -72.83)	-0.82 (-7.8, 6.1)	8.4 (1.5, 15.3)
Treatment effect (95% CI)	0.83 (-3.56, 5.21)		9.21 (-0.42, 18.8)	

CI: confidence interval; **LDH-N**: lactate dehydrogenase normalisation; **LS**: least squares; **LDH**: lactate dehydrogenase; **SD**: standard deviation; **n**: number; **%**: percentage; **PNH**: paroxysmal nocturnal haemoglobinuria; *Treatment effect: is estimated as the difference: ravulizumab – eculizumab except for percentage change in LDH and BTH rate where treatment effect is estimated as the difference: eculizumab – ravulizumab and for LDH normalisation that is estimated as odds ratio: ravulizumab versus eculizumab; **LDH-N was not a primary or key secondary outcome in the ALXN1210-PNH-302 trial, and 95% CIs were not estimated.

Open-label extension studies of the aforementioned trials, where all patients continue on or are switched to ravulizumab, demonstrated sustained treatment effect with ravulizumab up to week 104. The Review Group note limitations to the clinical evidence including the open-label design, small sample size, short duration of follow up for the randomised period (26 weeks), lack of efficacy data on mortality, and the generalisability of the trials to the Irish setting. The trials did not permit up-dosing of eculizumab which occurs in clinical practice, and the high proportion of Asian patients included is unlikely to be reflective of the Irish population.

2. Safety of ravulizumab

Ravulizumab has a similar safety profile to that of eculizumab, based on data collected in the two pivotal clinical trials. The overall incidence of adverse events (AEs) was similar between treatment groups (87.8% pooled ravulizumab versus 87.2% pooled eculizumab). The most commonly reported AEs (occurring in 10% or more of participants) were headache (32% pooled ravulizumab vs. 26.0% pooled eculizumab), nasopharyngitis (14.4% vs. 17.4%) and upper respiratory tract infection (14.0% vs. 7.8%). The majority of AEs were of grade one or grade two and a similar rate of grade three AEs was reported in both treatment arms (12.6% ravulizumab and 15.1% eculizumab). No deaths were reported in the 26-week period in either treatment group. The rates of AEs decreased in frequency in the open-label extension studies compared with the randomisation period. Fatigue was the most commonly reported AE across the 104-week period, followed by headache.

3. Cost effectiveness of ravulizumab

A cost-utility analysis was performed using a state transition model with a life-time horizon. Model cycle length was two-weeks. The modelled population is in accordance with the licensed indication for adults with PNH. Treatment effectiveness was determined by the

probability of experiencing a breakthrough haemolysis (BTH) event, depending on treatment-specific rates observed in the pivotal trials. The probability of requiring a transfusion and the mean number of red blood cells transfused was dependent on the treatment arm and the BTH health state occupied. Transition to death was possible from all living health states, and was modelled according to national mortality rates for the general population. Health-related quality of life (HRQoL) data collected during the trials were mapped to ED-5D-3L data to generate health-state utility values. The Applicant applied a utility increment (0.057) to the ravulizumab-treated arm, based on data obtained from a discrete choice experiment in the UK general population. The Review Group noted a number of limitations with the cost-utility analysis including: a small number of BTH events observed in the trials (rare outcome); a restriction of data informing transfusion requirements to randomised periods in the trials; and an assumption of a constant treatment effect over the model time horizon, which the Review Group consider to be uncertain.

The Review Group note that similar HRQoL results were observed between both treatments in the ravulizumab trials and did not consider it appropriate to apply an increment to the ravulizumab-treated arm in the NCPE-adjusted base case analysis. Further, the proportion of patients commencing the model in the treatment-naïve cohort and the treatment-experienced cohort were updated to reflect the most recent information available to the Review Group in the NCPE adjusted base-case analysis.

Results of the Applicant's base case, and the NCPE-adjusted base case, are illustrated in Tables 2 and 3, respectively.

Table 2: Results of the Applicant's deterministic incremental cost-effectiveness analysis of ravulizumab versus eculizumab.

Treatment	Total QALYs	Total Costs (€)	Incremental QALYs	Incremental Costs (€)	ICER
Ravulizumab	14.86	6,594,718	0.94	-621,262	Dominant
Eculizumab	13.92	7,215,980	-		

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life-year; **WTP**: willingness to pay;
ICERs presented are based on the list price of both drugs.
Note: Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied.

In the Applicant base case analysis, the probability of ravulizumab being cost-effective is

100% at both willingness-to-pay (WTP) thresholds of €20,000 and €45,000 per QALY.

Table 3: Results of the NCPE-adjusted base case deterministic incremental cost-effectiveness analysis of ravulizumab versus eculizumab.

Treatment	Total QALYs	Total Costs (€)	Incremental QALYs	Incremental Costs (€)	ICER
Ravulizumab	14.54	6,594,377	0.01	-620,118	Dominant
Eculizumab	14.54	7,214,495	-		

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life-year; **WTP**: willingness to pay;
Note: Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied. ICERs presented are based on the list price of both drugs.

The probability of ravulizumab being cost-effective compared with eculizumab in the NCPE adjusted base case is 52% at both WTP thresholds of €20,000/QALY and €45,000 per QALY, respectively. The Review Group anticipate that an eculizumab biosimilar product may become available in the next 18 to 24 months. The Review Group conducted hypothetical scenario analyses where the price to wholesaler (PTW) of a theoretical eculizumab biosimilar is 55% and 25%, respectively, of the originator product (Soliris®).

Table 4: Results of the scenario analyses (deterministic) of the NCPE adjusted base case incorporating potential eculizumab biosimilar products

Treatment	Incremental Costs	Incremental QALYs	ICER per QALY
Scenario 1			
Ravulizumab	€2,619,141	0.01	€433,541,798/QALY
Eculizumab biosimilar priced at 55% of originator product	-	-	-
Scenario 2			
Ravulizumab	€4,778,647	0.01	€791,001,017/QALY
Eculizumab biosimilar priced at 25% of originator product	-	-	-

ICER: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year; **WTP**: willingness to pay;
Note: Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied.

An analysis of the price-ICER relationship involving theoretical eculizumab biosimilar products indicates that a discount of 40% (scenario 1) to 80% (scenario 2) inclusive, on the current PTW of ravulizumab would be required in order for ravulizumab to be cost-effective relative to potential eculizumab biosimilar products.

4. Budget impact of ravulizumab

The PTW of ravulizumab is €4,936.18 (one 3mL vial containing 300 mg of ravulizumab (100 mg/mL)) and €18,099.33 (one 11mL vial containing 1,100 mg of ravulizumab (100 mg/mL). These are to be priced linearly if reimbursed in Ireland. The annual cost of ravulizumab per patient for the first year of treatment is €473,550 including VAT. The cost per annum from year two onwards is €435,603 including VAT. The Review Group identified several issues with the Applicant's budget impact model (BIM).

- The Review Group obtained more recent data (up to December 31st 2021) which indicated that there are currently 25 patients with PNH being treated with eculizumab, of which 20% are receiving the 1,200mg dose. The Applicant did not include the more up to date data in their model on request by the Review Group. The Review Group used the more recent patient data in the BIM.
- The Applicant has assumed that one new patient per year will initiate treatment. The Review Group consider the Applicant's estimate uncertain and conducted a scenario analysis varying the number of incident patients each year.
- The Applicant has assumed 100% market share for ravulizumab if reimbursed. This assumption favours ravulizumab. The Review Group assumed in the NCPE-adjusted BIM that patients on eculizumab 1,200mg will not switch to ravulizumab, as per clinical opinion.

Overall, the Review Group considers the budget impact estimates to be uncertain. The NCPE-adjusted five-year cumulative gross drug budget impact is estimated to be €51,043,041, with the five-year cumulative net drug budget impact estimated to be €530,944. The Review Group also acknowledge the predicted availability of a biosimilar eculizumab in the near future, which if reimbursed, will result in at least a 45% discount on the current PTW of eculizumab.

5. Patient submission

A patient organisation submission was received during the course of this assessment from PNH UK. It will be provided to the HSE and form part of the data that the HSE considers.

6. Conclusion

The NCPE recommends that ravulizumab (Ultomiris®), for the treatment of adult patients with PNH, be considered for reimbursement provided certain conditions are met*. These are that the cost of ravulizumab should not exceed any eculizumab products currently available or anticipated to be available in the near future. A price premium over eculizumab is not justified given that both treatments appear to have similar efficacy. In addition, ravulizumab did not demonstrate an improvement in treatment-related burden compared with eculizumab in clinical trials.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*