**Cost-effectiveness of ravulizumab (Ultomiris®) for the treatment of patients weighing at least 10kg with atypical haemolytic uraemic syndrome (aHUS), who are complement inhibitor treatment-naïve or have received eculizumab for at least three months and have evidence of response to eculizumab.**

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of ravulizumab (Ultomiris®) in patients with atypical haemolytic uraemic syndrome (aHUS), as per the product licence for ravulizumab. Following assessment of the Applicant's submission, the NCPE recommends that ravulizumab (Ultomiris®) not be considered for reimbursement unless cost-effectiveness can be improved relative to comparator treatments. 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** **July 2022**

**Summary**

In November 2021, Alexion Pharma UK submitted a dossier of the clinical effectiveness, cost effectiveness and potential budget impact ravulizumab (Ultomiris®) for the treatment of patients with atypical haemolytic uraemic syndrome (aHUS) as per the product licence. Alexion Pharma UK are seeking reimbursement for ravulizumab in the hospital setting.

aHUS is a rare, life-threatening disease of the blood. In aHUS, the complement system starts to attack the body's own cells, especially those that line the blood vessels. This leads to clots forming within the small vessels. The most commonly affected organ is the kidney but all organs can be affected. Left untreated it can be a life-threatening illness and the majority of people would develop end stage kidney failure. Thrombotic microangiopathy (TMA) episodes and response to such episodes (i.e. measures of haematologic parameters (platelet count and lactate dehydrogenase (LDH normalisation) and serum creatinine improvement) and improvement in renal impairment are used to estimate clinical response to treatment.

Ravulizumab is a monoclonal antibody that specifically binds to the complement protein C5, preventing the uncontrolled complement activation responsible for triggering aHUS disease activity (episodes of TMA). Ravulizumab was designed by re-engineering eculizumab (Soliris®) to achieve an extended half-life that is four times longer than that of eculizumab. Eculizumab is also marketed by the Applicant. Ravulizumab is formulated as a sterile concentrate for solution for intravenous (IV) infusion and the recommended dose is based on patient bodyweight. The recommended dosing consists of an initial loading dose followed by maintenance dosing, every eight weeks (in adults) or every four weeks (in paediatrics weighing <40kg), starting two weeks after the initial loading dose administration. For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered two weeks after the last eculizumab infusion, and then maintenance doses are administered once every eight weeks (in adults) or every four weeks (in paediatrics weighing <20kg), starting two weeks after loading dose administration. Ravulizumab treatment to resolve TMA manifestations should be for a minimum duration of six months, beyond which length of treatment is individually assessed. Patients at higher risk of TMA recurrence may require chronic therapy.

The current standard of care for patients with aHUS is eculizumab, another C5 inhibitor treatment. The dosing regimen for eculizumab in adult and paediatric patients (weighing ≥40kg) with aHUS consists of a four-week initial phase (900mg every week by IV infusion) followed by a maintenance phase (1200mg administered via IV infusion for the fifth week, followed by 1200mg every two weeks thereafter). In paediatric patients weighing less than 40kg, dosing is weight-based with initial loading dose phases of one or two weeks duration, followed by maintenance dosing every two weeks thereafter. The most recent data available to the Review Group indicated that, currently, there are 13 patients with aHUS being treated with eculizumab, of which eight are adults and five are paediatrics (one aged less than five years). The Applicant anticipates that all patients with aHUS currently being treated with eculizumab will switch and that all newly-treated complement inhibitor naïve patients will be first treated with eculizumab, and once stable, a switch to ravulizumab may occur.

## 1. Comparative effectiveness of ravulizumab

Clinical evidence is available from two phase three, open-label, single-arm, multicentre, international trials. ALXN1210-aHUS-311 (n=56) included adult patients with aHUS who were complement inhibitor treatment naïve and ALXN1210-aHUS-312 (n=28) included paediatric patients who were complement inhibitor treatment naïve (cohort one, n=18) and complement inhibitor treatment-experienced with eculizumab [for at least three months prior] (cohort two, n=10). Ravulizumab was assessed in both trials as per the recommended weight-based dosing regimen. The primary endpoint in both ALXN1210-aHUS-311 and ALXN1210-aHUS-312 was a complete TMA response (defined as normalisation of platelet count, normalisation of LDH and a ≥25% improvement in serum creatinine from baseline). Ravulizumab demonstrated improved outcomes at week 26 in both trials (Table 1).

**Table 1: Efficacy results for ALXN1210-aHUS-311 and ALXN1210-aHUS-312**

| **Trial** | **ALXN1210-aHUS-311** | **ALXN1210-aHUS-312** | |
|---|---|---|---|
| **Characteristics** | Ravulizumab (n=56) | Ravulizumab cohort 1 (n=18) | Ravulizumab cohort 2 (n=10) |
| Median age at first infusion, years (range) | 40.1 (19.5, 76.6) | 5.2 (0.5, 17.3) | 12.5 (1.2, 15.5) |
| **Primary outcome** | | | |
| **Complete TMA response*** n (%) [95% CI] | 30 (53.6) [39.6, 67.5] | 14 (77.8) [52.4, 93.6] | Not relevant (treatment-experienced) |

**CI**: confidence interval; **LDH**: lactate dehydrogenase; **n**: number; **%:** percentage; **aHUS**: atypical haemolytic uraemic syndrome; *Complete TMA response: defined as normalisation of platelet count (≥150 x $10^9$), normalisation of LDH (≤246 U/l) and a ≥25% improvement in serum creatinine. These criteria were to be met on two separate assessment obtained at least four weeks (28 days) apart (and any measurement in between) to meet the definition of complete TMA response.

Ongoing open-label extension studies of the aforementioned trials, where all patients continue on ravulizumab treatment, demonstrated sustained treatment effect with ravulizumab up to week 52. The Review Group note limitations to the clinical evidence including the open-label design, small sample size, lack of an active comparator arm, 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 Applicant conducted an indirect treatment comparison (ITC) with eculizumab which informs comparative effectiveness inputs. Results of the ITC indicate that ravulizumab is not as effective as eculizumab with regards to TMA response, the proportion of patients on dialysis at the end of the study and improvement in chronic kidney disease (CKD) stage, although results were not statistically significant. The Review Group noted a number of limitations with the ITC analysis including: a lack of patient-level data and inclusion of important baseline characteristics in the propensity score weighting method; small sample sizes; and the ten-year time difference in the clinical trial programmes. The Review Group consider the ITC results very uncertain. The Review Group note that ITC results are only relevant to the treatment-naïve population due to a lack of data available for both treatments in the treatment-experienced population.

**2. Safety of ravulizumab**

Ravulizumab has a tolerable safety profile based on data collected in the two pivotal clinical trials (26 week evaluation period) and ongoing open label extension studies (52 weeks of data). Nearly all patients reported at least one treatment emergent adverse event (TEAE). TEAEs of grade 3 and grade 4 were reported by 34 (45.9%) and 15 (20.3%) patients, respectively, most in adult patients, with the most commonly reported Grade 3 TEAEs in adults being hypertension (12%) and urinary tract infection (9%). End stage renal disease was the only Grade 4 TEAE reported in more than one patient. No events of meningococcal infections were reported in the evaluation period or extension period in either study. In total, four patients died in ALXN1210-aHUS-311 and there were no deaths in ALXN1210-aHUS-312. None of the deaths were considered study drug-related by the investigator. Four

patients discontinued treatment. The main concern with the safety profile is the limited database, especially for the subgroup of patients weighing<10kg, hence ravulizumab is not recommended for use in this population currently (15).

### 3. Cost effectiveness of ravulizumab

A cost-utility analysis was performed using a state transition model with a life-time horizon. There are four main health states (initiate treatment; discontinuation; relapse and re-initiation), with six living sub-health states (CKD stages progressing through to transplant) described within each main health state. Model cycle length was two weeks. The modelled population consists of adults and children weighing ≥10kg with aHUS who are complement inhibitor treatment-naïve. Thus, the modelled population is narrower than the licensed population. Consequently, the Review Group consider cost-effectiveness analysis results to be relevant for the treatment-naïve population only. The modelled populations were further categorised by transplant status: adult patients (non-transplant); adult population (prior transplant); and the paediatric population (non-transplant). Treatment effectiveness is modelled through the progression of patients through CKD stages and to transplant. The Review Group highlighted the limitations with the cost-effectiveness analysis including the small sample size informing the ITC outputs, uncertainty regarding discontinuation of complement inhibitors in Irish clinical practice and uncertainty regarding the relapse rate following discontinuation. The Review Group noted that assumptions relating to treatment discontinuation are important drivers of cost effectiveness as patients cannot enter the relapse and re-initiation health states, associated with additional costs, unless they discontinue treatment first. It should be noted that there are studies ongoing in the UK and the Netherlands where treatment with eculizumab is discontinued in patients who are demonstrating good renal response; potentially, this may be an option in Irish clinical practice in the future.

**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** | 14.95 | 5,033,603 | -1.14 | -1,227,618 | Less costly, less effective |
| **Eculizumab** | 16.09 | 6,261,221 | - | - | - |

**ICER**: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life-year;

ICERs presented are based on the list price of both medicines. Where a pairwise comparison demonstrates that ravulizumab is less costly, but less effective than eculizumab, the term 'less costly, less effective' is used. The ICER value for this analysis is in the south-west quadrant.
**Note:** Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied.

The Review Group implemented two changes to inform the NCPE adjusted base case analysis. The Review Group did not assume that patients would discontinue due to no renal recovery. The Review Group considered this to be already accounted for in the proportion of patients who are assume to be mis-diagnosed, receive treatment and subsequently discontinue once a different diagnosis is made. Secondly, an alternative distribution was chosen to extrapolate relapse data from the global aHUS registry. Results of the NCPE adjusted base case analysis are presented in Table 3.

**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** | 14.93 | 4,366,336 | -1.16 | -908,681 | Less costly, less effective |
| **Eculizumab** | 16.09 | 5,275,018 | - | - | - |

**ICER:** incremental cost-effectiveness ratio; **QALY:** quality-adjusted life-year;
ICERs presented are based on the list price of both medicines. Where a pairwise comparison demonstrates that ravulizumab is less costly, but less effective than eculizumab, the term 'less costly, less effective' is used. The ICER value for this analysis is in the south-west quadrant.
**Note:** Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied.

The Review Group anticipate that an eculizumab biosimilar product may become available in the next nine to 12 months. The Review Group conducted hypothetical scenario analyses where the price to wholesaler (PTW) of the eculizumab biosimilar is 55% and 25%, respectively, of the originator product (Soliris®).

**Table 4: Results of the hypothetical scenario analyses of the NCPE adjusted base case incorporating potential eculizumab biosimilar products**

| Treatment | Incremental Costs (€) | Incremental QALYs | ICER per QALY |
|---|---|---|---|
| **Scenario 1** | | | |
| Ravulizumab | 1,396,017 | -1.16 | Dominated |
| Eculizumab biosimilar priced at 55% of originator product | - | - | - |
| **Scenario 2** | | | |
| Ravulizumab | 2,932,482 | -1.16 | Dominated |
| Eculizumab biosimilar priced at 25% of originator product | - | - | - |

**ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year;
**Note**: Numbers are presented as rounded; calculations may not be directly replicable. A discount rate of 4% on costs and outcomes is applied.
Ravulizumab is dominated by eculizumab in the pairwise comparisons, meaning that ravulizumab is more costly and less effective than potential eculizumab biosimilar products.

Ravulizumab is dominated by eculizumab in both hypothetical scenario analyses, meaning ravulizumab is more costly and less effective than the eculizumab biosimilar products. Price-ICER analyses involving the eculizumab biosimilar products indicates that a discount of between 40% (scenario 1) up to 80% (scenario 2) on the current PTW of ravulizumab would be required for ravulizumab to be less costly than potential eculizumab biosimilar products.

## 4. Budget impact of ravulizumab

The PTW of ravulizumab is €4,936.18 (one 3mL vial) and €18,099.33 (one 11mL vial), which are to be priced linearly if reimbursed in Ireland. The annual cost of ravulizumab per adult 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 annual cost of ravulizumab per paediatric patient for the first year of treatment is €164,473 including VAT. The cost per annum from year two onwards is €158,401 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 13 patients with aHUS being treated with eculizumab, of which eight are adult patients and five are paediatric patients (one of which is less than five years old). The Applicant included this more recent data in their model on request by the Review Group at preliminary review.
- The Applicant has assumed one new patient per year initiating treatment. The Review Group consider the Applicant's estimate uncertain and conducted a scenario analysis varying the number of incident patients initiating treatment each year based on eculizumab-treatment approvals in Ireland. In the base case, increasing the number of incident patients initiating treatment annually decreases net drug budget impact estimates.
- Ravulizumab incorporates weight-based dosing for adults and children. This adds to the uncertainty of the estimates. The Applicant based estimates on a single weight band (adults between 60 and 100kgs), and following preliminary review included weight-based estimates for the paediatric population aged less than five years.

Overall, the Review Group considers the budget impact estimates to be uncertain. The five-year cumulative gross drug budget impact is estimated to be €33.69 million with the net drug budget impact estimated to be -€10.33 million. The Review Group also highlight the predicted availability of a biosimilar eculizumab in the near future (likely <12months), which if reimbursed, will result in at least a 45% discount on the current PTW of eculizumab. The five-year cumulative net drug budget impact of ravulizumab could potentially range between €5.77 million (45% discount) and €16.51 million (75% discount), depending on the discount associated with the eculizumab biosimilar. The presented budget impact estimates are uncertain as a result.

## 5. Patient submission

A patient organisation submission was received during the course of this assessment.

## 6. Conclusion

The NCPE recommends that ravulizumab (Ultomiris®), for the treatment of patients with aHUS weighing at least 10kg, not be considered for reimbursement unless cost effectiveness can be improved relative to comparator treatments*. Ravulizumab is less effective than eculizumab. This recommendation should consider the imminent introduction of eculizumab biosimilars. It is a condition of eculizumab reimbursement that patients will switch to a biosimilar product when it becomes available on the Irish market. Prescribers are required to confirm this in writing to the HSE Medicines Management Programme. Ravulizumab pricing should not exceed any eculizumab products currently available or anticipated to be available in the near future and the reduced efficacy relative to eculizumab should be considered in the improvement of cost effectiveness.

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