NCPE Assessment Summary

Ravulizumab (Ultomiris ®)

HTA ID: 25013

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Applicant: Alexion Pharma Inc.

Ravulizumab for the treatment of adult patients with neuromyelitis optica spectrum disorder who are anti-aquaporin 4 antibody positive

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of ravulizumab (Ultomiris ®) for the treatment of adult patients, with neuromyelitis optica spectrum disorder, who are anti-aquaporin 4 antibody positive.

Following assessment of the Applicant's submission, the NCPE recommends that ravulizumab (Ultomiris ®) not be considered for reimbursement for this indication*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Alexion Pharma Inc.) Health Technology Assessment of ravulizumab (Ultomiris ®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

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

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists 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 under consideration. 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.

Summary

In April 2026, Alexion Pharma Inc. submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of ravulizumab (Ultomiris ®) for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin 4 antibody positive (AQP4-IgG+ve). Alexion Pharma Inc. is seeking Hospital pricing approval of ravulizumab (Ultomiris ®) for this indication.

Ravulizumab is a monoclonal antibody that binds to the complement protein C5, thereby inhibiting the formation of the membrane attack complex, which plays a pivotal role in astrocyte destruction initiated by AQP4-IgG in NMOSD. Ravulizumab is administered as an intravenous infusion once every eight weeks, starting two weeks after loading dose. The loading and maintenance doses of ravulizumab are weight dependent and are outlined in the summary of product characteristics (SmPC). The SmPC does not specify any stopping criteria. The Applicant assumes that ravulizumab will be administered continuously long-term.

AQP4-IgG+ve NMOSD is a rare, severely disabling autoimmune disease of the central nervous system. The disease course is characterised by recurrent, severe relapses (attacks) of optic neuritis and/ or transverse myelitis, which result in the accumulation of neurologic disability and worsening of health-related quality of life (HRQoL). Relapses are unpredictable in their timing, duration, and severity. The main goals of therapy are to counteract acute attacks immediately, and to prevent further relapses. Standard of care maintenance therapy, in the prevention of relapses, in clinical practice in Ireland is rituximab monotherapy (used off label). Eculizumab is not reimbursed, in Ireland, for this indication. However, the Review Group consider that eculizumab might have been considered as a scenario comparator.

1. Comparative effectiveness of ravulizumab (Ultomiris ®)

The efficacy and safety of ravulizumab was assessed in CHAMPION-NMOSD; an open-label, single-arm trial which evaluated the efficacy and safety of ravulizumab alone or in combination (±) with immunosuppressants (ISTs) in participants with AQP4-IgG+ve NMOSD.

The placebo arm of the PREVENT trial (a randomised, double-blind, placebo-controlled trial which assessed the efficacy of eculizumab ± ISTs versus placebo ± ISTs in participants with AQP4-IgG+ve NMOSD), was used as an external control arm. The Review Group have concerns regarding the relevance of the placebo arm of the PREVENT trial as an external control arm, given that it does not represent standard of care in Ireland (i.e., rituximab monotherapy).

Relative efficacy and safety data from the primary analysis of CHAMPION-NMOSD and PREVENT (median (range) follow up 73.5 (11.0 to 117.7) weeks versus 36.0 (1.86 to 117.7) weeks respectively) were used to support the regulatory approval of ravulizumab. Updated efficacy and safety data from the final analysis of CHAMPION-NMOSD and PREVENT (median (range) follow up of 170.3 (11.0 to 243.0) weeks versus 36.0 weeks (1.9 to 208.6)) were also provided in the Applicant's submission. The primary endpoint was time to first adjudicated on-trial relapse (TTAR) as adjudicated by the Relapse Adjudication Committee (herein the RAC-TTAR). Secondary outcomes included the adjudicated annualised relapse rate (ARR) and clinically important changes from baseline on the Hauser Ambulation Index score (which quantifies mobility and gait changes). The Review Group note that relapse definitions and relapse severity subscales used in both trials have not been validated for AQP4-IgG+ve NMOSD.

Trial outcomes from CHAMPION-NMOSD and PREVENT (placebo arm) were evaluated using an unanchored population-adjusted indirect treatment comparison (ITC). The population-adjusted ITC results suggested that ravulizumab ± ISTs was associated with improvements in RAC-TTAR versus placebo ± ISTs at the primary analysis (hazard ratio (HR): 0.014, 95% CI 0.000 to, 0.103 p< 0.0001) which was sustained in the final analysis (HR: 0.011, 95% CI 0.000 to 0.0802, p< 0.0001). At the final analysis, no adjudicated on-trial relapses were observed in participants treated with ravulizumab ± ISTs, compared with 21 participants who had an adjudicated relapse in the PREVENT placebo ± ISTs group. The efficacy of ravulizumab based on RAC-TTAR was consistent across prespecified subgroups including geographic region, sex, age, baseline ISTs and prior use of rituximab. The adjudicated ARR of participants on ravulizumab ± ISTs was zero versus a historical comparator rate of 0.25. The Applicant states that an ARR comparison with the PREVENT placebo arm was not undertaken given the

differences in study design between CHAMPION-NMOSD and PREVENT. There were fewer patients who experienced clinically important changes from baseline Hauser Ambulation Index score with ravulizumab ± ISTs versus placebo ± IST (from PREVENT). There were no statistically or clinically meaningful differences between ravulizumab ± ISTs and placebo ± IST in HRQoL outcomes.

The Review Group consider that the use of an external control arm introduces confounding and selection bias that randomisation would otherwise protect against. The Review Group also note that an alternative comparator arm was used for the ARR outcome. The Review Group conclude that that treatment benefits with ravulizumab ± ISTs versus placebo ± ISTs may be overestimated.

Indirect treatment comparisons (ITCs) were required to provide comparative evidence for ravulizumab with standard of care in clinical practice in Ireland (i.e. rituximab monotherapy used off label). The RIN-1 study compared rituximab ± prednisolone (n=19) versus placebo ± prednisolone (n=19) in participants with AQP4-IgG+ve NMOSD. The Review Group concluded that the study populations were sufficiently similar to justify the ITC. Given there were no observed events (i.e., zero relapses) in the ravulizumab ± ISTs and rituximab ± prednisolone arms of CHAMPION-NMOSD and RIN-1 respectively, it is not possible to implement a reliable ITC.

2. Safety of ravulizumab (Ultomiris ®)

The safety of ravulizumab ± ISTs and placebo ±ISTs were reported from the final analysis of CHAMPION-NMOSD and the placebo arm from PREVENT respectively. The most commonly reported AEs with ravulizumab ± ISTs were headache (30.6%), upper respiratory tract infection (21.6%), nasopharyngitis (20.4%), diarrhoea (18.7%), pyrexia (17.7%), nausea (15%), arthralgia (14.4%), back pain (13.6%), fatigue (13.3%), abdominal pain (12.3%), dizziness (10.7%) and urinary tract infection (10.7%). Meningococcal infection was the only AE of special interest. The SmPC for ravulizumab outlines risk minimisation procedures including requirement for vaccination, and monitoring requirements for signs of meningococcal infection. Although all patients in CHAMPION-NMOSD were vaccinated prior to initiating treatment with ravulizumab, two participants experienced meningococcal

infection. The most commonly reported AEs in the placebo ± ISTs arm of the PREVENT trial were nausea (25.5%), headache (23.4%), urinary tract infection (21.3%) and pain in extremity (21.3%).

3. Cost effectiveness of ravulizumab (Ultomiris ®)

Methods

The modelled intervention in the Applicant's base case was defined as ravulizumab monotherapy. The modelled comparator was defined as a basket of ISTs either alone or in combination with rituximab (ISTs ± rituximab). The Applicant captured the cost of rituximab, however the efficacy of rituximab is not captured. The comparator arm therefore does not reflect standard of care in clinical practice in Ireland (i.e., rituximab monotherapy).

A Markov state transition model was developed in Microsoft Excel®, consisting of twenty-five health states defined by the cumulative number of relapses and an absorbing death state. The key efficacy inputs were implemented through deriving risk of relapse by fitting parametric curves fitted to TTAR data. Relapses were either 'disabling' or 'non-disabling' and were modelled to accrue a differential rate of Expanded Disability Status Scale (EDSS) progression. Patients were assumed to remain on treatment with ravulizumab, or ISTs ± rituximab for the model time horizon regardless of the number of relapses.

The Review Group had concerns with the Applicant's model structure. There is no robust evidence which quantifies the relationship between the modelled treatment effects (relapse rate) and disability (EDSS progression). EDSS is also primarily a measure of mobility and is considered biased toward ambulation which is only one aspect of a patient's disability in AQP4-IgG+ve NMOSD. Relapses can also result in sensory, visual, bladder and pain sequalae which can have a debilitating impact on HRQoL. The Review Group identified further substantial uncertainty in the cost effectiveness analysis. These included the assumption of persistent treatment effect with ravulizumab over the lifetime horizon and a treatment specific mortality benefit with ravulizumab, over ISTs (not substantiated by clinical data). The Applicant also implemented a multiplier for EDSS transitions for a disabling relapse which was not supported by robust data. The Applicant did not use HRQoL data collected in CHAMPION-NMOSD and PREVENT. Instead, health-state utility values were informed by a

study of a population with multiple sclerosis, conducted in Ireland. The Review Group considered these utility values to be highly uncertain. They were not identified systematically in line with NCPE requirements and are not considered generalisable to the target population.

Results

Results of the Applicant base case deterministic cost-effectiveness analysis are presented in Table 1. The Review Group note that the majority of the incremental QALY gain with ravulizumab is estimated from the extrapolated period (97%) rather than the observed clinical trial data (3%).

Table 1: Applicant base case incremental cost-effectiveness results [a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
ISTs ± rituximab	714,352	3.09	-	-	-
Ravulizumab	5,751,396	13.65	5,037,044	10.56	476,916

ICER: incremental cost-effectiveness ratio; **IST**: immunosuppressants **QALY:** quality adjusted life year
[a] Corresponding probabilistic ICER using 1,000 iterations =€486,952/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.
[b] A commercial in confidence Patient Access Scheme has been offered for ravulizumab not included in this table

The Review Group have a number of concerns regarding the reliability of results presented in the Applicant base case and the relevance of the comparator which does not reflect standard of care. The Review Group considered that the limitations of the evidence base underpinning cost-effectiveness estimates cannot be overcome by making adjustments to an NCPE adjusted base case. As such, the Review Group did not consider it appropriate to present an adjusted NCPE base case or a price-ICER analysis.

Sensitivity analysis

The Review Group conducted deterministic sensitivity analysis of individual key parameters in the Applicant's base case which were identified as being associated with considerable uncertainty. The model was most sensitive to; the assumption of persistence of treatment effect with ravulizumab over the lifetime of the model, the choice of EDSS bounds in the model structure, and the utility values.

4. Budget impact of ravulizumab (Ultomiris ®)

The price-to-wholesaler (PTW) for one pack of ravulizumab 300mg/mL (3mL vial) is €4,551.70 and ravulizumab 1,100mg/mL (11mL vial) is €15,689.56. The estimated total cost per patient for the first year of ravulizumab treatment is €404,714 (including VAT). The estimated total cost per patient for each subsequent year is €372,283 (including VAT).

There are no published prevalence or incidence data for AQP4-IgG+ve NMOSD in Ireland. Prevalence was estimated by clinical opinion in Ireland and validated by global data. Global incidence estimates were used to inform the number of patients diagnosed with AQP4-IgG+ve NMOSD in Ireland each year, which were validated by clinical opinion to the Applicant. The Applicant estimated that approximately 39 to 42 patients would be eligible for treatment with ravulizumab over a five-year period.

The estimated five-year cumulative gross and net drug-budget impact is approximately €45.1 (including VAT) and €44.6 million (including VAT). The Review Group consider that many of the inputs, in particular the market share estimates to be associated with considerable uncertainty. The Applicant estimates that ravulizumab would have a market share of 35% in Year One, increasing to 75% in Year Five. In an NCPE scenario whereby market share estimates are assumed to be 100% from Year One to Year Five, the estimated net drug-budget impact is approximately €73.7 million (including VAT). This scenario is subject to substantial uncertainty.

Ravulizumab was re-engineered from eculizumab and is considered similar, by the EMA, to eculizumab. The Review Group highlight the predicted availability of a biosimilar of eculizumab which may be available in Ireland in 2029 for the treatment of AQP4-IgG+ve NMOSD. If reimbursed by the HSE in this therapeutic indication, a biosimilar of eculizumab will result in at least a 45% discount on the 1st of October 2025 PtW of eculizumab (Soliris ®)

5. Patient Organisation Submission

A patient organisation submission was received. This submission will form part of the information that the HSE considers when making their drug funding decision.

6. Conclusion

The NCPE recommends that ravulizumab not be considered for reimbursement for the treatment of adult patients with NMOSD who are AQP4-IgG+ve *.

The Review Group note that the relative effectiveness of ravulizumab versus current standard of care (rituximab monotherapy, used off-label-label) was not determined. It is therefore unclear if ravulizumab works as well or better than rituximab in patients with AQP4-IgG+ve NMOSD. The Applicant's cost effectiveness analysis is highly uncertain. Ravulizumab is considerably more expensive than current standard of care (rituximab monotherapy) and it is associated with a substantial net drug budget impact.

*Next steps: The NCPE Assessment Report, recommendation and Patient Organisation submission, will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.
Further information on this process may be found here.