Re-evaluation of the cost-effectiveness of Eculizumab (Soliris®) for the treatment of Paroxysmal Nocturnal Haemoglobinuria (PNH) in the Irish Healthcare Setting

The NCPE has issued a recommendation regarding the use of eculizumab (Soliris®) for the treatment of paroxysmal nocturnal haemoglobinuria (PNH). The NCPE do not believe that eculizumab (Soliris®) is value for money for the treatment of patients with PNH in the Irish Healthcare setting.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out a re-assessment of the manufacturers (Alexion Pharma UK Ltd) economic dossier on the cost-effectiveness of eculizumab for the treatment of PNH. The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes 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 examine all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE.

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.

National Centre for Pharmacoeconomics **October 2013**

Summary

1. On the 21st February 2013 the National Centre for Pharmacoeconomics (NCPE) received a request from the HSE-Corporate Pharmaceutical Unit (CPU) to conduct a pharmacoeconomic evaluation of eculizumab (Soliris®) for the treatment of paroxysmal nocturnal haemoglobinuria (PNH). The manufacturer, Alexion Pharma UK Ltd submitted the full documentation to support the continued reimbursement of eculizumab on the 15th July 2013.

2. Eculizumab (Soliris®) is a humanized monoclonal antibody that blocks the activation of terminal complement at C5 and prevents the formation of C5a and the terminal complement complex C5b-9. It is indicated for the treatment of patients with paroxysmal noctural haemoglobinuria (PNH).

3. The NCPE completed a pharmacoeconomic evaluation of eculizumab on behalf of the HSE-CPU in February 2010 and concluded that the manufacturer failed to demonstrate that this product represented value for money for the treatment of PNH patients in the Irish healthcare setting. The HSE subsequently entered into an Access with Evidence Development (AED) agreement with Alexion Pharma UK Ltd to allow some time for additional evidence to be generated to inform long-term decision making over a period of three years. The AED agreement has now reached the pre-agreed end date and the HSE-CPU has commissioned the NCPE to re-evaluate the cost-effectiveness of eculizumab.

4. Alexion Pharma UK Ltd did not undertake a formal cost-effectiveness analysis. The submission included information in relation to PNH, product information for eculizumab, clinical evidence for the product, a budget impact analysis and a brief discussion of the economic impact.

5. The NCPE review of eculizumab that was conducted in 2010 includes a critical appraisal of the parent clinical studies (TRIUMPH and SHEPHERD) and the 102-week extension study investigating the rate of thromboembolic events (Hillmen et al. 2007). Further evidence consists of the additional extension studies from the parent clinical studies, a UK cohort study and retrospective data from the International PNH Registry.

6. The TRIUMPH study is the only double-blind, randomised, placebo controlled trial that demonstrates efficacy of eculizumab (n=87). Stabilisation of haemoglobin levels in the absence of transfusions was achieved in 49% of the patients assigned to eculizumab and none of those assigned to placebo. Eculizumab reduced intravascular haemolysis and improved patients quality of life (Hillmen et al. 2006).

7. The “SHEPHERD” study was an open label non placebo controlled single arm 52 week phase III trial (n=97). The primary efficacy endpoint was haemolysis as assessed by the AUC of LDH. The LDH was reduced from a mean of 2201 ± 105U/L at baseline to 297 ± 21U/L at 52 weeks.

8. Further evidence to support the clinical efficacy of eculizumab is derived from the uncontrolled 102 week extension study which evaluated the effect of eculizumab on thromboembolic events in patients with PNH (Hillmen *et al*. 2007). Patients from 3 independent clinical studies including a phase II pilot study and its extension, the TRIUMPH and SHEPHERD studies and the common phase III extensions, participated (n=187). The thromboembolic event rate with eculizumab treatment was reported as 1.07 events/100 patient years as compared with 7.37 events/100 patients years prior to eculizumab therapy. The NCPE review group highlighted the limitations associated with this uncontrolled study.

9. Evidence of the long-term effect of eculizumab on incidence of renal dysfunction or damage in patients with PNH was derived from the open-label phase III extension study of the three parent clinical studies (n=187) (Hillmen *et al*. 2010). During the course of 18 months of treatment, eculizumab-treated patients were six times more likely to have improved renal function in all chronic kidney disease (CKD) stages, with 34% showing improvement in renal function. The uncontrolled nature of this study was highlighted as a limitation by the NCPE review group.

10. In 2013, Hillmen et al. published further evidence from the extension study of the long term safety and efficacy of eculizumab in patients with PNH over 66 months. All patients showed a reduction in LDH levels (median reduction of 86.9% at 36 months). Thrombotic events decreased by 81.8%, with 96.4% remaining free of thrombosis. An improvement or stabilisation in CKD was demonstrated in 93.1% of patients.

Transfusion independence increased by 90% from baseline, with the number of red blood cells transfused decreasing by 54.7%. Four patient deaths were reported that were unrelated to treatment, resulting in a 3-year survival estimate of 97.6%. The NCPE review group highlighted that this is a non-controlled clinical study. Furthermore, this study was underpowered to show a significant improvement in patient survival.

11. Evidence of the long-term efficacy of eculizumab was reported from a single centre cohort study in the UK (n=79) conducted between 2002 and 2009. A historical control group of 30 patients who fulfilled the criteria for eculizumab in the 7 years prior to the availability of eculizumab were used for the survival analysis. Survival of patients on eculizumab was also compared with age- and sex-matched control averages from the UK population data. The authors reported no significant difference in survival between the eculizumab group and the age and sex-matched control averages from the UK population. The 5-year survival rate for the historical control group (66.8%; 95%CI 41.4%-85.1%) was significantly worse than the patients treated with eculizumab (95.5%; 95%CI 87.6%-98.5%). The NCPE review group highlighted that the baseline demographic and clinical characteristics of cases and historical controls are not statistically compared in this study. Confounding factors, including time bias, do not appear to have been appropriately adjusted for. Furthermore, this study was underpowered to detect any significant difference in mortality between the treatment group and the age and sex- matched normal population.

12. Finally, the long term effects of eculizumab in patients with PNH outside the clinical trial setting was examined in a retrospective observational study from the International PNH Registry (n=1047). Multivariate analysis demonstrated that eculizumab had a significant protective effect against occurrence of thrombosis (HR 0.23; 95%CI 0.08-0.66 P=0.0053) and preventing mortality (HR 0.41; 95%CI 0.23-0.73). The NCPE review group have concerns that there is the potential for selection bias and residual or unmeasured confounding as a result of the observational nature of this study that may not have been adequately controlled for.

13. In summary, there is evidence that eculizumab treatment in adults with PNH reduces transfusion requirements and weaker evidence that it reduces risk of thrombosis,

renal failure and mortality. Furthermore, evidence of clinical benefit of eculizumab in the treatment of patients with PNH is limited to patients with a history of transfusions.

14. The NCPE evaluation that was conducted in 2010 included a description of the West Midlands Health Technology Assessment Collaboration (WMHTAC) health economic data for the cost-effectiveness of eculizumab. The NCPE are not aware of any additional published economic evaluations of eculizumab since this time. As the previous NCPE report highlighted, none of the ICERs derived from the WMHTAC model are anywhere near the level that would be considered cost effective or value for money.

15. The budget impact assessment that was submitted by Alexion Pharma was performed over a five year time horizon. The total number of patients expected to receive eculizumab increases from 13 in 2013 to 20 in 2017. The total cost (including 23% VAT) per patient per year on maintenance treatment (i.e. receiving 78 vials per year) is €437,247. The total annual gross budget impact (including 23% VAT), assuming the standard maintenance dose is administered to all eligible patients ranges from €5.1 m in 2013 to €8.2 m in 2017. The cumulative gross budget impact over 5 years is estimated at €33 million.

16. At a price of €4,557.50 per 300mg/30ml vial and a total cost of €437,247 per patient per year we do not believe that eculizumab (Soliris®) is value for money for the treatment of patients with PNH in the Irish Healthcare setting. Alexion Pharma UK Ltd. did not include an economic model as part of their submission and failed to demonstrate the cost-effectiveness of this therapy.