All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Eculizumab (Soliris®▼) for the treatment of paroxysmal nocturnal haemoglobinuria

Alexion Pharma UK Ltd

Advice No: 0509 – April 2009

Recommendation of AWMSG

Eculizumab (Soliris®▼) is recommended for restricted use within NHS Wales according to agreed guidelines for the treatment of paroxysmal nocturnal haemoglobinuria.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 29th April 2009

The recommendation of AWMSG is:

Eculizumab (Soliris®▼) is recommended for restricted use within NHS Wales according to agreed guidelines for the treatment of paroxysmal nocturnal haemoglobinuria.

Additional notes:

- AWMSG recommends that eculizumab (Soliris®▼) should only be used on an individual patient basis according to agreed guidelines.
- AWMSG considers that eculizumab (Soliris®▼) satisfies the AWMSG criteria for ultra orphan drug status.
- The All Wales Therapeutics and Toxicology Centre (AWTTC) reviewed this appraisal recommendation in December 2022.

ABBREVIATIONS

AWMSG	All Wales Medicines Strategy Group
BCSH	British Committee for Standards in Haematology
DVT	Deep vein thrombosis
EPAR	European Public Assessment Report
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
INR	International normalised ratio
ITT	Intention-to-treat
IV	Intravenous
LYG	Life years gained
NHS	National Health Service
NMG	New Medicines Group
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SC	Standard care
SCT	Stem cell transplant
SPC	Summary of Product Characteristics
ULN	Upper limit of normal reference range
WMP	Welsh Medicines Partnership

2.0 PRODUCT DETAILS

2.1 Licensed indication
Eculizumab is indicated for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH)[1].

Evidence of clinical benefit of eculizumab in the treatment of patients with PNH is limited to patients with history of transfusions[1].

2.2 Dosing
To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients must be vaccinated at least two weeks prior to receiving eculizimab and must be re-vaccinated according to current medical guidelines for vaccination use[1].

After dilution, eculizumab is administered as an intravenous (IV) infusion over 25-45 minutes. Patients should be monitored for one hour following infusion. The dosing regimen consists of a five-week initial phase followed by a maintenance phase[1]:

- Initial phase: 600 mg of eculizumab every week for the first four weeks, followed by 900 mg of eculizumab for the fifth week of the initial phase.
- Maintenance phase: 900 mg of eculizumab every 14 ± 2 days.

The Summary of Product Characteristics (SPC) for eculizumab states that it may be administered to patients aged 65 years and over although experience in this patient population is still limited. It also states that there is no experience in children and the safety and efficacy of eculizumab have not been studied in patients with renal or hepatic impairment. See the SPC for full details[1].

2.3 Market authorisation date
20 June 2007[2].

2.4 UK Launch date
Eculizumab has been available in the UK since August 2007.

3.0 DECISION CONTEXT

PNH may occur at any age, with median age at diagnosis of 30 to 40 years. It is a rare, genetically acquired disease that arises due to mutation of the PIG-A gene in a bone marrow stem cell[3]. This results in a deficiency or absence of certain cell surface proteins that protect red blood cells (RBCs) from attack by the complement immune system. Chronic intravascular haemolysis occurs, which is associated with serious complications. These may range from fatigue, erectile dysfunction and recurrent abdominal pain, through to potentially life threatening states of anaemia, pulmonary hypertension, hepatic and renal failure, development of acute myeloid leukaemia and bone marrow failure. Median survival following diagnosis of PNH has been estimated as 10-16 years, with premature death occurring primarily due to thromboses. Standard treatments are supportive, including blood transfusions for the management of anaemia and thromboprophylaxis with warfarin or heparin[3]. Allogeneic haematopoietic stem cell transplantation (SCT) is currently considered the only potentially curative therapy. Few PNH patients have been treated in this way because of the high risks involved and the scarcity of suitable donors[3]. It is estimated that 15-25% of patients may experience spontaneous long-term remission many years after diagnosis[3].

Eculizumab is the first licensed agent for the treatment of PNH. It is a humanised monoclonal antibody that inhibits the activation of terminal complement. This inhibits the complement-mediated intravascular haemolysis[1]. The number of patients in Wales meeting the licensed indication for eculizumab is estimated by the company to be 46[4]. The company, however, anticipates that eculizumab will be reserved for use in the most severely affected patients (15%); therefore seven patients in Wales. It has been designated as an orphan medicinal product by the European Medicines Agency (EMEA), and meets the All Wales Medicines Strategy Group (AWMSG) criterion for ultra-orphan status, as it is intended for a condition affecting no more than 1 in 50,000 persons in the UK (i.e. 60 persons in Wales) at the time of submission[5]. No evidence was presented to suggest that eculizumab will provide a bridge to a definitive (potentially curative) therapy, such as SCT.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

A 26-week, randomised, double-blind, phase III trial (n=87) demonstrated that eculizumab treatment significantly reduced surrogate markers of haemolysis and resulted in improvements in anaemia as indicated by increased haemoglobin stabilisation and reduced need for RBC transfusions, compared with placebo. An open-label, 52-week, phase III study, conducted in 97 patients with lower pre-treatment transfusion requirements than in the placebo-controlled study, provided consistent results with eculizumab treatment however, this was an uncontrolled study. Both studies also found significant improvements in health-related quality of life and measures of fatigue. An uncontrolled, long-term, extension study (n=195) also demonstrated that the incidence of thromboembolic events was significantly reduced during treatment with eculizumab compared with the period before eculizumab treatment, including patients who were receiving antithrombotic therapy. The most frequent adverse events in the studies were headache, nasopharyngitis, back pain, nausea and fatigue. No patients are reported to have developed neutralising antibodies following therapy with eculizumab, and infusion-related reactions occurred at a similar frequency as in placebo-treated patients. There were no discontinuations or deaths due to adverse events.

4.2 Review of the evidence on cost-effectiveness

The company has not submitted a Welsh-specific economic analysis in support of eculizumab. Instead, the company submission comments on a West Midlands Health Technology Assessment Collaboration (WMHTAC) report on eculizumab and PNH that was published in April 2008. The authors of this report considered that there was insufficient data to conduct a full, comprehensive assessment of the cost effectiveness of eculizumab. Therefore, three 'preliminary' cost-effectiveness analyses were conducted to generate estimates of:

i) the cost per stabilisation of haemoglobin and the cost per stabilisation of lactate dehydrogenase for eculizumab versus no eculizumab treatment

ii) the cost per year gained (LYG) for a variety of costs of standard care (SC) and cost of SC avoided by treatment with eculizumab

iii) the cost/LYG for averting thrombosis-related mortality with eculizumab

There are many limitations to these analyses. The measures of effectiveness do not appropriately address or reflect the impact of the disease state of PNH, nor its treatment with SC or eculizumab. The incremental cost effectiveness ratios generated in the analyses are based on incomplete costs and inadequate outcome measures, which limits their interpretation in the context of the wider use of NHS resources. The estimates of the incremental cost effectiveness ratio, included in the company submission, range from £0.6 million to £1 million per life-year gained in analysis (ii), which assumes that eculizumab returns survival of patients to that of the general population.

5.0 LIMITATIONS OF DECISION CONTEXT

- No studies have been conducted in patients with hepatic impairment, which is important given that this is a potential complication of PNH. Data in patients with renal impairment are limited to *post hoc* analyses of the available trial data.
- The economic evidence presented in the company submission is severely limited.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

The main efficacy data in the company submission are from a 26-week, randomised, double-blind, placebo-controlled phase III study (TRIUMPH study)[6], a 52-week, single-arm, phase III study (SHEPHERD)[7], and a 104-week open-label, single-arm, extension study involving patients from the phase III studies and a small pilot study[8]. All participants in these studies had a history of transfusions. Details are summarised in Table 1, Appendix 1, and are discussed below. A *post hoc* analysis of the impact of eculizumab treatment on renal function[9] in all patients in these studies is also provided and is discussed briefly in section 7.2.

6.1 Clinical efficacy

6.1.1 TRIUMPH placebo-controlled, 26-week trial

This study provides the only comparative data for eculizumab[1,6]. A total of 87 patients (35 men and 52 women) met the inclusion criteria and had a median of around 17-18 units of packed red blood cells (PRBC) transfused in the 12 months before the trial and a mean lactate dehydrogenase (LDH) level – a surrogate marker of haemolysis - in excess of 2,000U/L at baseline (normal range 103 to 223U/L[8]). There were two specified primary endpoints (based on intention to treat analysis): stabilisation of haemoglobin (Hb), which was the proportion of patients maintaining an individualised Hb level above that which led to their last transfusion, and units of PRBC transfused over the 26-week treatment period. Eculizumab was administered as per the SPC[1,6].

Eculizumab was significantly superior to placebo for stabilisation of Hb, achieved in 21 out of 43 (49%) eculizumab recipients compared with none of the 44 patients in the placebo group ($p<0.001$). The median number of PRBC units transfused over the course of treatment was zero in the eculizumab group versus 10 units in the placebo group ($p<0.001$) (mean number of units 3.0+/-0.7 versus 11.0+/-0.8, respectively).

Patients were stratified at randomisation by the number of PRBC units transfused in the previous 12 months (4 to 14 units; 15 to 25 units; >25 units)[2]. In patients who received eculizumab, the proportion achieving Hb stabilisation was numerically greater in the lowest stratum (12 out of 15 patients, 80%) than in the middle (5 out of 17, 29.4%) and the highest (4 out of 11, 36.4%) strata. Hb stabilisation was statistically significantly different between the eculizumab and placebo in the lower and middle strata ($p<0.001$) but not in the higher stratum ($p=0.09$). However, the difference in the mean number PRBC units transfused over the 26 weeks was statistically significantly different in all strata. It should be noted that number of patients in each stratum is low, which warrants caution in the interpretation of these data[2].

Eculizumab was also significantly superior for the pre-specified secondary endpoints of independence from transfusion (51% versus 0%, $p<0.001$), haemolysis as measured by LDH area under the curve, and fatigue as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue instrument[6] (see table 1, Appendix 1). FACIT-Fatigue scores increased (improved) by 6.4 in the eculizumab group and decreased (worsened) by 4.0 points in the placebo group, giving an overall difference of +10.4 points with eculizumab. The baseline scores are not provided, but the minimally important difference in scores is thought to be between three to four points on this instrument scale[10].

Points to note

- Due to the small sample size and relatively short duration of treatment, this study does not provide comparative data on the effects of eculizumab on thrombotic events[1].
- Improvements in LDH from baseline and the FACIT-Fatigue scores were observed from as early as week 1 of treatment.
- Pre-specified exploratory analyses included assessment of health-related quality of life (HRQoL) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). This indicated that eculizumab was associated with significantly improved scores in terms of global health status and functioning, and the majority of the subscales relating to symptoms, compared with placebo[6].
- Other endpoints included time to first transfusion, Hb changes and free Hb at the end of the study, all of which significantly favoured eculizumab treatment compared with placebo.

6.1.2 SHEPHERD uncontrolled 52-week study

This non-comparative study[7] enrolled 97 patients (median age 41 years) with lower pre-treatment transfusion requirements than those enrolled in the TRIUMPH study[6], although baseline LDH levels were similar. The primary endpoint was haemolysis as measured by LDH area under the concentration curve (AUC). The secondary endpoints were haemolysis as measured by LDH change from baseline and fatigue as measured by FACIT-Fatigue[7]. Additional endpoints included quality of life measured by the EORTC QLQ-C30.

A total of 96 patients completed the 52-week study. Compared with pre-treatment, after 52 weeks of treatment the LDH AUC was statistically significantly reduced ($p<0.001$)[7]. Median LDH levels were 269U/L compared with a pre-treatment level of 2,052U/L ($p<0.001$). The mean improvement in FACIT-Fatigue score was +12.2 points ($p<0.001$). Other, exploratory endpoints also showed significant improvements with eculizumab treatment. These included a reduction in the median (mean) number of PRBC units transfused, from eight (12.3) in the previous 12 months to zero (5.9) units whilst on treatment. Overall, 51% of patients achieved transfusion independence over

the 52 weeks. Even though there was a significant reduction in the number of PRBC units transfused, there was a significant rise in Hb level, from a median of 9.3g/dL at baseline to a median of 10.2g/dL at 52 weeks ($p<0.001$). There was also a reduction in median free Hb from 34.9mg/dL at baseline to 5mg/dL at 52 weeks ($p<0.001$), and improved HRQoL scores in global health status and functioning, and the majority of the subscales relating to symptoms on the EORTC QLQ-C30 questionnaire[7].

Points to note

- In addition to permitting inclusion of patients with lower pre-treatment transfusion requirements than in TRIUMPH, this study also allowed patients with evidence of thrombocytopenia to participate[7]. The percentage of participants who had thrombocytopenia is not clear from this study.
- These data are limited due to the uncontrolled nature of the study. They are, however, consistent with the 26-week comparative data from TRIUMPH, despite the differences in baseline transfusion requirements.
- The median change in LDH AUC increased and the proportion of patients achieving transfusion independence decreased with increasing baseline LDH level. However, these are based on baseline LDH quartiles, involving 25 or fewer patients per quartile[7].

6.1.3 Uncontrolled, 102-week extension study

From the TRIUMPH, SHEPHERD and a small pilot study, 187 out of a possible 195 patients entered this extension study to determine the effect of treatment of eculizumab on the incidence of thrombotic events in PNH[8]. Patients who had received placebo in the TRIUMPH study were switched to eculizumab. The cumulative thromboembolic event rate during the 102 weeks of treatment with eculizumab was compared with that determined retrospectively from the period between diagnosis with PNH, or first thrombotic event, and first treatment with eculizumab. Thromboembolic events were defined by Major Adverse Vascular Event (MAVE) criteria, which include thrombophlebitis/deep vein thrombosis, pulmonary embolus, cerebrovascular accident, amputation, myocardial infarction, transient ischemic attack, unstable angina, renal vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis, gangrene, acute peripheral vascular occlusion, sudden death, and a category for other events[8].

In the period before eculizumab treatment, the thromboembolic event rate was 7.37 events per 100 patient-years of observation. During eculizumab treatment, the event rate was significantly lower at 1.07 events per 100 patient-years ($p<0.001$). The pre-treatment period provided 1,683.4 patient-years of observation, compared with 281.0 patient-years for the eculizumab treatment period. When the time period considered before treatment was set equal to that whilst on treatment, the respective number of thromboembolic events was 39 and 3 ($p<0.001$)[8].

An analysis was provided in only patients who were taking antithrombotic agents. In the period before eculizumab treatment, the thromboembolic event rate was 10.61 events per 100 patient-years of observation, compared with 0.62 events per 100 patient-years whilst on eculizumab treatment ($p<0.001$). When restricted to patients taking anticoagulants, the event rates were 11.54 versus 0.72 per 100 patient-years, respectively ($p<0.001$)[8].

Points to note

- These data are limited due to the uncontrolled nature of the study. No data are provided in relation to PRBCs transfused and markers of haemolysis (the key efficacy outcomes for the TRIUMPH and SHEPHERD studies) over the long term.
- Around 53% of patients received antithrombotics, of which the vast majority received anticoagulants, during and before the study. Pre-eculizumab treatment thromboembolic event rates were somewhat higher in patients taking anticoagulants (11.54 events per 100 patient-years) than in all patients (47% of who were not taking any form of antithrombotic agent). It is reported that thromboembolic event rates increased in the 12 months before eculizumab treatment, and in the placebo-group during the 6-month TRIUMPH study period, which is interpreted by the study authors to mean that the improvements in thromboembolic event rates following eculizumab treatment are unlikely to be due to improved use of anticoagulation[8]. However, it is not clear what proportion of patients who received anticoagulants achieved adequate anticoagulation (e.g. INR levels within therapeutic range), or experienced haemorrhagic adverse events, in either the pre-eculizumab treatment period or the eculizumab treatment period.
- Around 85% of thromboembolic events in the pre-treatment period were venous thromboses (primarily deep vein thromboses of the lower extremities, mesenteric/splenic vein and hepatic/portal vein thromboses), and the remainder were arterial (cerebrovascular accident/transient ischaemic attack 13.7%, myocardial infarction/unstable angina 1.6%)[8]. There are no data provided to determine whether the magnitude of the reduction in thromboembolic events observed during eculizumab treatment is the same or different across different types of thromboembolic events.

6.2 Safety

Comparative safety data are available only against placebo from the 26-week TRIUMPH study[6]. The adverse effects reported most commonly at a numerically higher incidence with eculizumab than placebo included headache (44% versus 27%), nasopharyngitis (23% versus 18%), back pain (19% versus 9%), nausea (16% versus 11%) and fatigue (12% versus 2%)[6]. There were no significant differences in the incidence rates between the two groups for any reported adverse event and there was no evidence of an increased incidence of infections with eculizumab[2]. Serious adverse events were reported in 13 patients: four in the eculizumab group and nine in the placebo group. None were considered to be treatment-related, and no patients died during the study[6].

The pattern and incidence of adverse events with eculizumab treatment was similar in the SHEPHERD study[7]. There are no safety data from the 104-week extension study presented in the company submission[4]. The EPAR notes that the serious adverse event incidence rates for patients who were enrolled in TRIUMPH and had accumulated six months of exposure in the extension study were generally similar compared to those observed in the TRIUMPH eculizumab and placebo treatment groups[2]. Overall, there were few discontinuations of eculizumab in any of the studies and none were considered to be probably due to eculizumab treatment[2].

As with all therapeutic proteins, there is a potential for immunogenicity with eculizumab[1]. No patients have been reported to develop neutralising antibodies following therapy with eculizumab, and there has been no observed correlation of antibody development to clinical response or adverse events, although it is noted that specific antibody detection techniques require further development[2]. Infusion reactions occurred at similar frequency as in the placebo-treated patients[2].

Due to its action on the complement immune system, eculizumab treatment is anticipated to increase the risk of meningococcal infection. All patients should be vaccinated at least two weeks prior to receiving eculizimab. In the clinical study programme there have been three reported cases of meningococcal infection in eculizumab-treated patients, two of which were in vaccinated PNH patients[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator treatments

Standard care (SC) for patients with PNH may include a wide range of agents and interventions, including blood transfusions, anticoagulants, analgesics, as well as interventions to treat complications such as renal and hepatic dysfunction. Currently, there are no specific comparators for eculizumab.

7.2 Comparative effectiveness

- PNH is a rare disorder that is associated with significant morbidity and premature death. Eculizumab is the first agent to be specifically licensed for the treatment of PNH.
- Eculizumab is an ultra-orphan drug as defined by the AWMSG criteria[5], and comparative data are limited to a small, 26-week, phase III trial conducted against placebo[6]. This demonstrated that eculizumab significantly reduced surrogate markers of haemolysis and resulted in improvements in anaemia as indicated by increased Hb stabilisation and reduced need for PRBC transfusions compared to placebo. An open-label, 52-week, phase III study, conducted in patients with lower pre-treatment transfusion requirements than in the placebo-controlled study, found consistent results with eculizumab treatment, albeit that this was an uncontrolled study that compared these outcomes in the period before and during eculizumab treatment[7].
- Thrombosis is a major complication of PNH and is the leading cause of death in patients[3]. An uncontrolled, long-term, extension study demonstrated that the incidence of thromboembolic events was significantly reduced during treatment with eculizumab compared with the period before eculizumab treatment, including in patients who were receiving antithrombotic therapy[8]. However, there are no data provided to determine whether the magnitude of the reduction in thromboembolic events observed during eculizumab treatment is the same or different across different types of thromboembolic events. There are also no direct survival data available for eculizumab.
- Other outcomes assessed in the studies included HRQoL and fatigue scores, which also improved significantly in patients receiving eculizumab compared with the pre-treatment period[7] and placebo[6].

- Renal impairment as a result of haemolysis is also a complication of PNH. The company submission includes details of a *post hoc* analysis of available study data, which suggests that treatment with eculizumab may improve or help stabilise renal function[9]. Of 195 patients in the analysis, 40 (21%) had chronic renal insufficiency at initial screening (glomerular filtration rate [GFR] < 60 ml/min/1.73 m^2). In these patients, GFR remained stable (median increase 0.47 ml/min/1.73m^2) and 10% of patients were no longer classified as having chronic renal insufficiency following eculizumab treatment[9]. However, details are limited and these findings would require further confirmation.
- The company anticipates that eculizumab will be reserved for use in the most severely affected patients (estimated to be 15% of PNH patients)[4]. The available data include patients with a broad range of pre-treatment transfusion requirements and degrees of haemolysis.
- During eculizumab treatment there was an increase in the proportion of PNH type III RBCs in patients[6]. Although not observed in the clinical studies, the possibility of serious rebound haemolysis upon withdrawal of eculizumab treatment cannot be excluded[4].
- As a therapeutic protein, there is the potential for development of neutralising antibodies following therapy with eculizumab, and infusion-related reactions[1]. No patients are reported to have developed neutralising antibodies following therapy with eculizumab, and infusion-related reactions occurred at similar frequency as in placebo-treated patients[2].
- There were very few discontinuations in the studies; the vast majority (96%) completed the parent studies and then entered the long-term extension study[8].
- Due to its mode of action, patients must be vaccinated against meningococcal disease at least two weeks before receiving eculizumab treatment. The risk management plan agreed with the EMEA specified that the drug will only be made available to a patient after written confirmation has been provided that the patient has effectively received meningococcal vaccination[2]. A patient card system to provide details of the signs and symptoms of infection and instructions to seek medical care immediately was also agreed[2].

8.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issue for AWMSG to consider is whether any additional benefits offered by eculizumab (Soliris®) over the relevant comparator(s) justify any additional costs and, if so, whether the total budgetary impact of supporting the use of eculizumab is acceptable.

8.2 Description and critique of the company's submission

The company has not submitted a Welsh-specific economic analysis in support of eculizumab. Instead, the company submission[4] comments on a West Midlands Health Technology Assessment Collaboration (WMHTAC) report on eculizumab and PNH that was commissioned by the West Midlands Specialised Commissioning Team and was published in April 2008[3]. This report contains what are described as three 'preliminary' cost effectiveness analyses, as a systematic review of the literature failed to identify appropriate data to conduct a comprehensive economic study. The authors consider that the major parameters of cost and benefit required to build a decision analytical model for the cost-effectiveness of eculizumab versus SC can be identified but there is a lack of reliable quantitative information about these parameters. The report concluded that implementation of a fully informed model for estimation of cost-effectiveness in terms of incremental cost per QALY gained is impractical at this time[3].

The three analyses were conducted to generate estimates of[3]:

i) the cost per stabilisation of haemoglobin and the cost per stabilisation of lactate dehydrogenase (a marker of intravascular haemolysis – the cause of signs and symptoms in PNH) for eculizumab versus no eculizumab
ii) the cost per life year gained (LYG) for a variety of costs of SC and cost of SC avoided by treatment with eculizumab
iii) the cost/LYG for averting thrombosis related mortality with eculizumab.

i) The cost per stabilisation of haemoglobin and the cost per stabilisation of lactate dehydrogenase for eculizumab versus no eculizumab

The WMHTAC report[3] describes a simplistic cost-effectiveness analysis based on the 26-week data from the phase III, double-blind, placebo-controlled, TRIUMPH trial[6] (discussed in section 6). The first-year acquisition cost of eculizumab at the recommended dosing schedule would be £252,000[3,4]. The cost of treatment in the 26 weeks of the TRIUMPH trial is therefore estimated as £126,000. Over this period, 49% of patients in the eculizumab group achieved and maintained haemoglobin values at a level above which transfusion would be required, compared with 0% in the placebo group ($p<0.001$)[6]. Over the same period, 37% of patients achieved normalisation of lactate dehydrogenase (LDH) levels with eculizumab treatment, compared with 0% on placebo ($p<0.001$)[6].

The incremental cost per haemoglobin level stabilised with eculizumab compared with no eculizumab treatment is therefore estimated as £257,142 (i.e. £126,000/0.49). The incremental cost per normalisation of LDH is estimated as £340,541. On the basis that a significant reduction in LDH levels, rather than only normalisation, may yield clinical benefit, a further analysis has been conducted to determine the incremental cost per reduction in LDH to less than two times the upper limit of normal range of LDH. The incremental cost for this outcome is reported as £132,492 for treatment with eculizumab versus no eculizumab treatment[3].

The company submission notes that this analysis does not consider any savings in the costs of SC as a result of eculizumab treatment[4]. It therefore asserts that these estimates should be adjusted downwards[4]. However, the extent of downwards adjustment that would be appropriate is unclear. The WMHTAC report indicates that the costs of SC are unknown[3], and later explores the impact of assumed costs within the range £1,000 to £100,000[3]. The actual magnitude of any reduction in SC costs likely to be achieved by the use of eculizumab is also unclear.

ii) The cost per year LYG for a variety of costs of SC and cost of SC avoided by treatment with eculizumab

The WMHTAC report[3] states that it is clear that PNH is life threatening and that the major potential benefit of eculizumab treatment is likely to be an extension of life expectancy. It notes that there is no direct evidence about the impact of eculizumab on mortality but considers that, based on estimates of the reduction in rates of thrombosis with eculizumab, reductions in mortality rates could be substantial. Using natural history studies of European PNH cohorts, it reports that, on average, over 25 years PNH claimed between about 10.2 and 4.5 years of life relative to the general population. Assuming that survival of patients receiving SC and who are eligible for eculizumab treatment lies somewhere between the extremes reported for these European cohorts, and that eculizumab treatment returns survival to that of the general population, then over a 25 year time horizon the corresponding cost of eculizumab drug

provision/LYG is estimated to be between £0.6 million and £1 million (discounting both costs and LYG at 3.5%, and setting annual eculizumab cost £245,700/patient)[3].

As there are no published estimates for the costs of SC and the savings to be had in SC from the use of eculizumab, different scenarios of SC costs and the magnitude of the reductions in these were explored. When the annual cost of SC was assumed to be between £1,000 and £100,000 per patient, savings in these were assumed to be between 50% and 90%, and the life years saved over a 25 year span were taken to be between 10.2 and 4.5 years, the estimated incremental cost per LYG ranged from £0.5 million to £1.4 million (costs and benefits discounted at 3.5%). The ICER was more sensitive to cost of SC when LYG were small (4.5 years) and savings high (90%)[3].

The company submission[4] notes that the natural history study cohorts consisted of all diagnosed patients, rather than the 15% of patients that it considers is sufficiently haemolytic to warrant eculizumab treatment. The company considers that survival in this 15% of patients would be lower than in the overall patient cohorts. It also states that the rates of thrombosis at baseline in the eculizumab trials (31.3%) was higher than the rate in patients at presentation in one of the natural history studies reported as 7.2% in the company submission.

In terms of the range of ICER values reported in this analysis, the company submission states that the ICER of £1.4 million/LYG is generated using an expected life years saved with eculizumab treatment of only 4.5 years (discounted), which it considers to be outside of the plausible range[4].

iii) The cost/LYG for averting thrombosis-related mortality with eculizumab

The WMHTAC report[3] describes a simple decision-analytic model of the use of eculizumab or non-use of eculizumab in the prevention of thrombosis-related death. The costs of SC are not considered. A time horizon of 10-15 years (based on reported median [not mean] survival times) is used and a discount rate of 3.5% is applied to both cost and LYG.

Thrombosis rates were estimated from a long-term, open-label extension study involving patients from the phase III trials (TRIUMPH and SHEPHERD) and a pilot study (total n=195). The thrombosis rate with eculizumab treatment was compared with the pre-treatment rate in the same patients. With eculizumab treatment this was 1.07 events/100 patient-years compared with 7.37 events/100 patient-years prior to eculizumab treatment ($p<0.001$)[8]. Mortality rates of 52% for patients with thrombosis, and 15% for patients without thrombosis were used, based on pooled median results from several studies.

In patients with a history of transfusions (patients such as those in the eculizumab trials) the ICERs ranged from £1.2 million/LYG when median survival was assumed to be 15 years, to £1.4 million/LYG when median survival was assumed to be 10 years[3].

The WMHTAC report also includes a sensitivity analysis in which all PNH patients (with or without a history of transfusions) are considered. The thrombosis rate for all diagnosed PNH patients was estimated in this report to be 4.22 per 100 patient-years for patients without use of eculizumab, and the thrombosis rate for all PNH patients treated with eculizumab was taken to be 0.61 per 100 person-years (the same relative risk as that for PNH patients with a history of transfusions [1.07/7.37=0.15] was applied). At an assumed median survival of 15 years the ICER is estimated as £2.8 million/LYG, and at 10 years is estimated as £3.2 million[3].

The company submission[4] highlights that, whilst thrombosis is a major cause of death in patients with PNH, it is not the only cause and this analysis fails to consider other causes of PNH-related death. There is also no consideration given to the potential reduction in the costs of SC as a result of treatment with eculizumab. It also questions the precision of the point estimate of mortality for patients without thrombosis, given that the 95% credible interval around this estimate is so wide. Finally, the company highlights that the sensitivity analysis using all PNH-diagnosed patients does not represent the expected use of eculizumab, which is anticipated to be used only in a sub-population with the most severe disease[4].

AWMSG summary of the economic evidence presented for eculizumab

There are many grave limitations to the economic evidence based on the above analyses and presented in the company submission. In brief, the measures of effectiveness used in the above analyses do not appropriately address or reflect the impact of the disease state of PNH, nor its treatment with SC or eculizumab. The ICERs that are generated are essentially based on incomplete costs and inadequate outcome measures, which limits their interpretation in the context of the wider use of NHS resources.

Eculizumab meets the AWMSG criteria for ultra-orphan drug status[5]. There is no evidence presented that eculizumab will provide a bridge to a definitive (potentially curative) therapy.

8.3 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost-effectiveness of eculizumab beyond the WMHTAC report[3].

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

Literature-based estimates of prevalence and incidence, and mortality estimates inferred from rates of thrombosis, are combined with Welsh population estimates to produce estimates of the net number of patients with PNH in Wales. Based on expert opinion, it is assumed that around 15% of patients will have haemolytic disease of sufficient severity to warrant treatment with eculizumab. The costs of SC, and the degree to which savings in SC costs will be achieved with the use of eculizumab is unknown. Hypothetical scenarios of cost savings with eculizumab have been explored, which yield more than a five-fold difference in the net budget impact estimates presented in the company submission. As such, these estimates are not likely to be reliable or informative.

The company submission notes that, currently, two patients are known to be receiving eculizumab in Wales, and have been for several years. The budget impact associated with the use of eculizumab in these patients has simply being estimated as the annual cost of treating two patients with eculizumab (£491,400). The company will fund delivery and home administration of eculizumab through a third party.

9.2 Perspective and time horizon

The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years[4].

9.3 Data sources

9.3.1 Incident and prevalent cases

Data from a retrospective study of patients with PNH in the Yorkshire region are used to provide prevalence (1.59/100,000 over 15 years) and incidence (0.13/100,000/year) rates[12]. Using these figures, and the assumption of a Welsh population of 2.9 million, the company estimates that there are 46 patients with PHN in Wales, and around four new cases each year. The WMHTAC report[3] refers to estimates of thrombosis rates as being 1.07 per 100 person-years for patients treated with eculizumab and 7.37 per 100 person-years for patients pre-eculizumab treatment. Thrombosis is considered to be responsible for 45% of PNH-related deaths, and on this basis the company suggests that around two patients die each year. The net number of patients with PNH is therefore estimated as 46 in year 1 (prevalent cases only), and rises by two patients per year to 54 patients in year 5. It is assumed that all diagnosed patients would be receiving some kind of treatment[4].

9.3.2 Projected rate of adoption and market share

On the basis of expert clinical opinion expressed in the WMHTAC report[3], the company submission states that around 15% of PNH patients would be sufficiently haemolytic to warrant treatment with eculizumab. Using the assumptions above, in years 1-3 this would amount to 7 patients per year being treated with eculizumab, rising to 8 patients per year in years 4 and 5[4]. However, the company also states that, currently, only two patients are known to be receiving eculizumab in Wales, both of whom participated in eculizumab clinical trials and have been using eculzimab for several years[4].

9.3.3 Costs and resource use

The company will fund the storage, delivery, reconstitution and home administration of eculizumab through a third-party homecare provider[4]. Therefore, only the drug acquisition costs are counted in these estimates. In the first year of treatment, at the recommended dose, the cost is £252,000 per patient. In subsequent years, this is £245,700, due to the fact that the first year of treatment involves an initiation phase[1,4].

Determination of the net budget impact requires knowledge of the costs of SC that would potentially be displaced by the use of eculizumab. The costs of SC are unknown, as is the magnitude of their displacement. Therefore, the company has adopted an approach used in the WMHTAC report, in which several hypothetical levels of cost savings are considered: £1,000, £10,000, £100,000 and £200,000[3]. This hypothetical range of SC savings is very wide and it is unclear how realistic these would be.

9.4 Results

Based on the two patients who are known to be receiving eculizumab in Wales currently, the company suggests that the budget impact is known to be £491,400 (i.e. 2 patients @ £245,700)[4].

Based on the net number of patients predicted using the data from the literature, and the hypothetical scenarios of SC cost savings, there is more than a five-fold difference between the upper and lower net budget impact estimates presented in the company submission (see Table 1A). It should be noted that these estimates assume an annual drug acquisition costs of £245,700 per patient, which relates to the second and subsequent year costs (i.e. the additional £6,300 associated with the initial phase of eculizumab treatment in each new patient is not considered).

Table 1A. Company estimates of possible net drug budget impact from use of eculizumab[4]

	Net budget impact	
Hypothetical standard care cost savings	**Years 1-3 (7 patients treated/year)**	**Years 4 & 5 (8 patients treated/year)**
£1,000	£1,712,900	£1,957,600
£10,000	£1,649,900	£1,885,600
£100,000	£1,019,900	£1,165,600
£200,000	£319,900	£365,600

9.5 Sensitivity analysis
No further analyses have been conducted for the budget impact estimates.

9.6 Comparative unit costs
SC for patients with PNH may include a wide range of agents and interventions, including blood transfusions, anticoagulants, analgesics, as well as interventions to treat complications such as renal or hepatic dysfunction. Currently, there are no specific comparators for eculizumab.

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements
- There appear to be no national guidelines on the diagnosis and management of PNH. In 2006, the British Committee for Standards in Haematology (BCSH) issued guidelines on oral anticoagulation (warfarin), which recommended long-term anticoagulation with a target international normalised ratio (INR) of 2.5 for patients with large PNH clones (PNH granulocytes >50%) and a platelet count greater than 100 x 10^9/L. Anticoagulation was also recommended for consideration in patients with smaller clones and platelet counts less than 100 x 10^9/L dependent on additional risk factors for thrombosis and bleeding[13]. The BCSH also issued guidelines on the diagnosis and management of aplastic anaemia in 2008, which detailed the tests to detect (exclude) PNH[14].
- Eculizumab should be administered under the supervision of a physician experienced in the management of patients with haematological disorders[1]

10.1.1 Other points
- The company is funding a PNH registry, which will enrol all patients with PNH, regardless of the treatment they receive. This will record treatment history and outcomes, and data will be made available for publication[4].
- The company will fund delivery and infusion of eculizumab using a third-party homecare provider[4].

10.2 Related advice
None

10.3 Previous AWMSG/NICE advice
None

10.4 Ongoing studies

The company submission does not include details of any ongoing studies that will report results in the next six to 12 months beyond the PNH registry that it has established[4].

10.5 Patient organisation information

An individual patient submission was provided to AWMSG members.

GLOSSARY

Incidence:
The rate at which new cases occur in a population during a specified period[15].

Prevalence:
The proportion of a population that are cases at a point in time[15].

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Appendix 1. Additional Clinical Information

Table 1. Prospective studies of eculizumab in PNH

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics*		Treatment regimens	Outcomes
1,6 TRIUMPH	Randomised, double-blind, placebo-controlled, phase III trial 26-week treatment period	87 patients randomised (1:1)	Aged ≥18 years ≥4 blood transfusions in previous 12 months (≥1 in 13 weeks pre-randomisation) and mean Hb ≤10.5g/dL pre-transfusion PNH type III erythrocyte ≥10% Platelet count ≥100,000/mm^3 LDH ≥1.5 x ULN	Eculizumab n=43. Females 47%. Mean age 42 years. Median PNH duration 4.3 years. History of aplastic anaemia 19%. History of thrombosis 21%. Concomitant use of anticoagulant 56%. Median PRBC transfused in previous 12 months 18 units. Mean pre-treatment LDH 2,199.7 U/L. Free Hb 40.5mg/dL.	Placebo n=44. Females 66%. Mean age 38 years. Median PNH duration 9.2 years. History of aplastic anaemia 27%. History of thrombosis 18%. Concomitant use of anticoagulant 46%. Median PRBC transfused in previous 12 months 17 units. Mean pre-treatment LDH 2,258.0 U/L. Free Hb 46.2mg/dL.	Eculizumab at the licensed dose of 600mg IV once weekly for 4 weeks, then 900mg IV once for 1 week, then 900mg IV once every 2 weeks, up to week 26 vs. Placebo IV at the same frequency as eculizumab	**Primary endpoints (ITT analyses):** **Stabilisation of Hb (Hb above individualised set point)†:** Eculizumab 21/43 (49%) versus placebo 0/44; p<0.001 **Units of PRBC administered:** Eculizumab (median) 0 versus placebo 10; p<0.001 (Mean number of units 3.0 versus 11.0) **Secondary endpoints:** **Transfusion independence:** Eculizumab 22/43 (51%) versus placebo 0/44; p<0.001 **Haemolysis as measured by LDH AUC:** Eculizumab 58,587U/L versus placebo 411,822 U/L; p<0.001 (Mean LDH: Eculizumab 327.2 U/L versus placebo 2,418.9U/L; p<0.001) **Fatigue as measured by FACIT-fatigue tool (mean change in score from baseline):** Eculizumab +6.4 versus placebo -4.0; difference +10.4 points; p<0.001

Table 1. Continued

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics*	Treatment regimens	Outcomes
1,7 SHEPHERD	Single-arm phase III study 52-week treatment period	97 patients enrolled	Aged ≥18 years ≥1 blood transfusions in previous 2 years PNH type III erythrocyte ≥10% Platelet count ≥30,000/mm^3 Neutrophil count ≥500/microL LDH ≥1.5 x ULN	Females 50.5%. Mean age 41 years. Median PNH duration 4.9 years. History of aplastic anaemia 30%. History of thrombosis 43%. Concomitant use of anticoagulant 61%. Median PRBC transfused in previous 12 months 8 units. Median pre-treatment LDH 2,051 U/L. Free Hb 34.9mg/dL.	Eculizumab at the licensed dose of 600mg IV once weekly for 4 weeks, then 900mg IV once for 1 week, then 900mg IV once every 2 weeks, up to week 26	**Primary endpoint (ITT analyses):** **Haemolysis as measured by LDH AUC at 52 weeks compared with baseline** Mean change -632,264; p<0.001‡ **Secondary endpoints:** **Haemolysis as measured by LDH at 52 weeks:** Median 269 U/L; p<0.001‡ **Fatigue as measured by FACIT-fatigue tool (mean change in score from baseline):** Eculizumab +12.2; p<0.001‡
2,8 Extension study	Single-arm, 104-week extension study involving patients from TRIUMPH, SHEPHERD and a small pilot study	195 patients (including 11 from pilot study)	-Clinical trial participants included all patients in the three eculizumab PNH clinical studies (n=195) [6-8].	- 103 patients on antithrombotics (91 on anticoagulants)	Ongoing treatment with eculizumab 900mg IV once every 2 weeks, up to week 102 (Patients from placebo arm of TRIUMPH commenced eculizumab as licensed and entered this study)	**Per 100 person-years rate of thrombotic events over 104 weeks of treatment compared with pre-eculizumab treatment:** 1.07 events versus 7.37 events; p<0.001 (3 events over 281 person-years versus 124 events over 1683.4 person-years) **Equalised pre- and on-treatment time period:** 3 events versus 39 events; p<0.001 **In patients on antithrombotics:** 0.62 events per 100 person-years versus 10.61 events per 100 person-years; p<0.001

AUC=Area under the concentration curve; FACIT-fatigue tool= Functional Assessment of Chronic Illness Therapy- Fatigue instrument (scores can range from 0 to 52, with higher scores indicating improvement in fatigue. Difference of 3-4 points thought to be minimally important difference[10]); Hb=Haemoglobin; LDH=Lactate dehydrogenase – a surrogate marker of haemolysis (normal range 103 to 223 U/L); PRBC=Packed red blood cells; ULN=upper limit of normal range; *No statistically significant difference reported between baseline characteristics of placebo group and eculizumab group in the TRIUMPH study[6]; † Each patient was assigned an individual transfusion algorithm according to their 12 month pre-trial transfusion history. The Hb level at the time of qualifying transfusion during the last 13 weeks before randomisation defined the Hb set point against which the primary endpoint was assessed[6]; ‡ p-value versus baseline values[7].