Technology Assessment Report No. 209

Preliminary Economic Analysis on eculizumab for paroxysmal nocturnal haemoglobinuria (PNH)

Date: May 2013

Summary of Proposal

Pharmaceutical Eculizumab (Soliris®)
Supplier Alexion
Proposed Indication Paroxysmal nocturnal haemoglobinuria (PNH)
Dosing 600 mg weekly for 4 weeks, 900 mg in week 5, then 900 mg fortnightly ongoing
Pharmaceutical Price [redacted] per 300 mg vial, including a [redacted]% discount, $25,700 per fortnight First year cost of $686,000, subsequent years approximately $670,000
Current Treatment Best supportive care including blood and platelet transfusions and anticoagulation

Executive Summary

This preliminary Technology Assessment Report (TAR) assesses the cost-effectiveness of eculizumab plus best supportive care compared with best supportive care in patients with paroxysmal nocturnal haemoglobinuria (PNH) who meet the proposed criteria as defined below:

- Have a clone size >50%, have systemic symptoms (for example severe abdominal pain, fatigue and shortness of breath) and there is evidence of active haemolysis; OR
- Have developed thrombosis despite adequate treatment (for example anticoagulation).

The cost-utility analysis range is approximately 0.4 – 0.9 QALYs gained per $1 million invested ($1,100,000 – $2,500,000 per QALY). This is based on incremental gains of 9.2 QALYs with incremental costs of $11.4 million over a patient's life time.

This analysis models the cost-effectiveness of eculizumab for patients with PNH who meet the criteria outlined by the Pharmacology and Therapeutics Advisory Committee (PTAC) and the Haematology Subcommittee. If the analysis was to be widened to include all patients with PNH who could benefit from treatment with eculizumab the average QALY gain per patient would be lower.

PNH is a rare disease and impacts greatly on a patient's quality of life, with symptoms such as severe anaemia, abdominal pain, and anxiety due to the risk of a thrombotic event. There is currently no funded alternative for patients with PNH as bone marrow transplants are not considered because of the high risk of mortality associated with them. Patients currently receive blood and platelet transfusions as well as anticoagulants to try to reduce the risk of a thrombotic event and improve their health related quality of life. Although stem cell transplants can cure PNH, the mortality risk associated with the transplant is considered too high when compared with not having a transplant.

The key clinical trial evidence has been reviewed by PTAC and the Haematology Subcommittee. PTAC considered the quality of evidence was excellent in supporting a reduction in transfusions, reduced haemolysis and improved haemoglobin levels, good in supporting improved fatigue and quality of life, and fair/moderate in reducing thrombosis rates. However, PTAC considered the evidence to be poor or inadequate to support that eculizumab prolongs survival or improves renal and cardiac function. After considering all decision criteria, PTAC recommended a decline priority, given the extremely high cost per patient.

Consistent with the requirements of PHARMAC's Prescription for Pharmacoeconomic Analysis (PFPA), the base case analysis has the following key inputs: a life time horizon for treatment, clinically significant benefit from treatment and therefore quality-adjusted life year (QALY) gains, life expectancy from the age of treatment commencement until death of approximately 20 years with best supportive care and 25 years in patients receiving eculizumab and best supportive care, based on a notional relative risk of 1.25. We have assumed that patients who receive eculizumab have a quality of life score of 1, whereas patients who receive current treatment have a quality of life score of 0.535, based on expert clinical advice.

Initial induction therapy consists of 600 mg eculizumab weekly for 4 weeks, 900 mg in week 5. Patients then receive a dose of 900 mg eculizumab per fortnight by infusion, continuing as lifelong therapy. The price per 300 mg vial of eculizumab is [redacted] (after a [redacted] % discount proposed by the supplier), which is a yearly cost of approximately $670,000 per patient. Costs and benefits are discounted annually at 3.5%.

The price of eculizumab is the key driver in the model. At the proposed price of eculizumab, the CUA result is not very sensitive to the other variables that are included in the model. Even with a 50% price reduction for eculizumab, this remains the case.

If we receive a new commercial agreement from the supplier, we may update the economic model to take into account further details which enhance the modelling and make it more realistic. With a significant price reduction we expect that the model will become more sensitive to other variables. Such analysis may include the following:

- additional health states showing the deterioration over time in patients with PNH;
- proportion of patients who benefit from treatment with eculizumab;
- greater clarity regarding the quality of life of these patients;
- impact of adverse effects of eculizumab;
- the proportion of patients that are likely to receive benefit from eculizumab;
- possible long-term safety impacts of receiving eculizumab; and
- costs and savings associated with blood transfusions and the infusion cost of eculizumab that are not currently included in the model.

1 Context

1.1 Proposal Under Assessment

An application for the funding of eculizumab for paroxysmal nocturnal haemoglobinuria (PNH) was received from Alexion Pharmaceuticals in November 2011. The application did not include a cost-utility analysis (CUA).

The Pharmacology and Therapeutics Advisory Committee (PTAC) reviewed the application for eculizumab for PNH in February 2012. The Committee recommended the proposal be declined for listing on the Pharmaceutical Schedule and referred the application to the Haematology Subcommittee of PTAC. The Haematology Subcommittee convened in August 2012 and recommended the proposal with a low priority. In February 2013 PTAC reviewed the minutes from the Haematology Subcommittee meeting and decided to re-review all evidence, including new information provided by Alexion in February 2013, before making a recommendation. In March 2013 PTAC recommended the proposal be declined.

Minutes of the following meetings are included below; the March 2013 PTAC teleconference minutes, the February 2013 PTAC minutes, the August 2012 Haematology Subcommittee minutes and February 2012 PTAC minutes.

March 2013 PTAC Teleconference Minutes

Application

1.1 The Committee reviewed an application from Alexion Pharmaceuticals for the listing of eculizumab (Soliris) on the Pharmaceutical Schedule for the treatment of paroxysmal nocturnal haemoglobinuria (PNH).

Recommendation

1.2 The Committee after considering all the decision criteria **recommended** that the application for eculizumab (Soliris) in paroxysmal nocturnal haemoglobinuria (PNH) be declined on the basis of high cost per patient.

1.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

1.4 The Committee noted that the purpose of the teleconference was to review its previous recommendation (February 2012) for eculizumab. The Committee noted that at its February 2012 meeting PTAC had recommended the application to list eculizumab be declined and the application be referred to the Haematology Subcommittee for consideration.

1.5 The Committee noted that the Haematology Subcommittee met in August 2012 and recommended eculizumab be listed in the Pharmaceutical Schedule with a low priority subject to criteria limiting it to patients with paroxysmal nocturnal haemoglobinuria (PNH) who:

- Have a clone size >50%, have systemic symptoms (for example severe abdominal pain, fatigue and shortness of breath) and there is evidence of active haemolysis; OR
- Have developed thrombosis despite adequate treatment (for example anticoagulation).

The Haematology Subcommittee also considered that given the high cost of treatment, an advisory panel may be required to administer the treatment eligibility criteria.

1.6 The Committee noted additional evidence had been reviewed by the Haematology Subcommittee in August 2012 which had not been reviewed by PTAC at its last meeting. The Committee noted that following publication of the minutes of the earlier meetings, correspondence had been received from the supplier, Alexion Australia, in response to both the February 2012 meeting PTAC minutes and the August 2012 Haematology Subcommittee minutes. Professor Peter Hillmen, Consultant Haematologist and Professor of Haematology, University of Leeds had also responded to the February 2012 PTAC minutes.

1.7 The Committee noted that no new clinical trials specifically relating to eculizumab were presented but that the supplier's response to the Haematology Subcommittee meeting made reference to some clinical studies relating to PNH in general and other treatments for PNH like anticoagulation.

1.8 Overall, the Committee considered that the quality of evidence to support that eculizumab reduced transfusion requirements, reduced haemolysis and improved haemoglobin levels, was excellent. There was also good evidence that it improved fatigue and quality of life. The Committee considered that the evidence to support that eculizumab reduced thrombosis rates were of moderate/fair quality. However, the Committee considered that there was poor or inadequate evidence to support the claims that the treatment prolongs survival in patients or improves renal and cardiac function.

1.9 The Committee noted that there is no comparative evidence of bone marrow transplants (BMT) versus eculizumab in PNH. The Committee noted that in New Zealand, the standard international protocol for allogeneic transplants is followed for BMTs in general, and current success rates are in line with international standards. The Committee noted that because PNH is relatively rare, there is a lack of robust evidence for BMT in this indication. The Committee noted the 5 year probability of survival at 5 years of 68% (standard error +/-3%) with transplant. Treatment related mortality is 32% mainly from infection and graft versus host disease (de Latour et al. Haematologica 2012; 97(11): 1666-1673). The Committee noted that PNH patients in New Zealand are not routinely transplanted unless they develop aplastic anaemia, for which there are separate treatment protocols to PNH.

1.10 The Committee considered that warfarin anticoagulation is not an alternative to eculizumab treatment in PNH but there is good evidence that it does reduce thrombosis risk (Hall et al. Blood 2003;103:3587-3591). The Committee considered that the risks with warfarin anticoagulation quoted by the supplier from Palareti et al study (Lancet 1996;348:423-428) (overall risk of 7.6 bleeding complications over 100 patients-years, with the risk increasing to 11.0 during the first 90 days of treatment) was too high and the study population was not reflective of the PNH population who are generally younger.

1.11 The Committee noted that the supplier quoted results from the Hillmen paper (Hillmen et al. Blood 2007;110:4123-4128) to support the efficacy of eculizumab over warfarin anticoagulation. The Committee noted that no confidence intervals were presented for the difference in thrombosis rates, and there was no analysis of interaction between reduction in thrombosis rates and treatment with an anticoagulant. The Committee also considered it was unclear if "immortal time bias" was accounted for in the analysis (where subjects have to remain event free until start of exposure to be classified as exposed, and incorrect consideration of this unexposed time period causing bias). Other potential sources of bias which may have inflated the estimates of thrombosis rates on warfarin are that those on warfarin may have been started on it because of an increased risk of thrombosis or because they had presented with PNH by having a thrombosis, both forms of reverse causation bias. For the latter the paper by Hall (Hall et al. Blood 2003; 102:3587) found that about 5% of those with PNH presented with thrombosis. Both of these would inflate the apparent risk of thrombosis on warfarin. The Committee considered that these factors, alongside the reduction in thrombosis rates seen in this paper, may be biased in favour of eculizumab.

1.12 The Committee considered that there were no alternative treatments to eculizumab other than bone marrow transplants, and noted that transplants were associated with a significant risk of mortality and morbidity. The Committee considered that warfarin was an additional rather than a replacement treatment. The Committee also noted that patients would need to be vaccinated for meningitis and receive penicillin prophylaxis whilst on treatment. The Committee noted that about 50% of patients would still require blood transfusions whilst on eculizumab treatment due to on-going haemolysis.

1.13 The Committee noted that patients who were treated with eculizumab achieved improvements in their quality of life that were clinically important. The Committee noted that there was evidence from one RCT and a few cohort studies with measurements of up to two years of changes in Functional Assessment of Chronic Illness Therapy) (FACIT)-fatigue and European Organisation for Research and Treatment of Cancer (EORTC)-total scores that were clinically meaningful.

1.14 The Committee considered that it is likely that there would be an overall survival benefit for patients being treated with eculizumab, but did not consider that there is sufficiently robust data to estimate the

extent of this benefit. The Committee noted the paper by Kelly et al (Blood 2011;117:6786) which reported the survival of 79 patients receiving eculizumab matched with age and sex-matched normal populations. The Committee noted there was no statistically significant evidence of changes in survival but this does not mean that there is positive evidence that survival rates are the same. The Committee noted that no long term data is available, but considered that it is likely that someone with PNH would have a lower life expectancy than expected for normal populations of the same age/sex even with eculizumab treatment and therefore considered the benefit is overstated in the Kelly et al 2011 paper. The Committee noted that aplasia would continue to be a cause of mortality in this patient group because there is no evidence that eculizumab slows progression to aplasia. The Committee noted that in a small number of patients, the PNH clones spontaneously resolve with or without eculizumab treatment.

1.15 The Committee noted that all patients with PNH could benefit from treatment with eculizumab although in clinical studies indicate that about 66% respond better than others who still require on-going blood transfusions (Kelly et al. Blood 2011;117:6786). The Committee agreed with the finding of the Haematology Subcommittee that the patients most likely to benefit from treatment with eculizumab would be those with a clone size of >50% based on the Hall et al study (Blood 2003;102:3587-3591). The Committee noted that although the 50% cut-off was somewhat arbitrary, the study indicated that patients with PNH granulocytes >50% (including those on primary warfarin prophylaxis) had a 10-year cumulative incidence rate of thrombosis of 34.5% compared with those with clone sizes smaller than 50% who had a thrombosis rate of 5.3% ($p<0.01$). The Committee disagreed with the supplier's estimate that restricting eculizumab to those with a clone size >50% would only exclude one patient from accessing treatment based on the proposed algorithm. The Committee considered that limiting it to those with clone size >50% would likely halve the number of patients who would qualify and allow targeting of treatment to those most likely to benefit given the treatment's high cost.

1.16 The Committee agreed with the treatment algorithm proposed by the supplier except for the clone size cut-off and it considered that all patients who develop severe aplastic anaemia should be excluded from receiving eculizumab treatment. The Committee noted that it might be possible to word the Special Authority criteria for eculizumab without the need for an assessment panel but considered that PHARMAC was the appropriate body to decide how to administer the access criteria for eculizumab.

1.17 The Committee considered that it would maintain its previous recommendation to decline this funding application for eculizumab in PNH, following review of all the evidence available. The Committee considered that while there is evidence that eculizumab does provide a clinical benefit, the cost of the pharmaceutical is so high that it has crossed the threshold of what is acceptable, thus making the funding of the treatment unjustifiable in terms of cost relative to all other therapies. The Committee considered that its recommendation also takes into account the uncertainty remaining about the treatment's long term safety and the survival benefit it confers.

February 2013 PTAC Minutes

4.3.3. Regarding item 3, the Committee noted that it had previously recommended that the application for eculizumab be declined; however, the Haematology Subcommittee had recommended it for funding with a low priority. The Committee considered that in light of the Subcommittee's differing recommendation, additional evidence the Haematology Subcommittee had seen and the recent correspondence from the supplier, it would need to re-review all evidence before making a recommendation. The Committee noted the recent public interest regarding eculizumab and considered that a teleconference would ensure a more timely response rather than waiting for the May PTAC meeting. The Committee recommended that PHARMAC staff arrange this meeting for mid to late March and considered that it would be beneficial to have some members of the Haematology Subcommittee present to provide its expert opinion on paroxysmal nocturnal haemoglobinuria and its treatments.

August 2012 Haematology Subcommittee minutes

3 Eculizumab in Paroxysmal Nocturnal Haemoglobinuria

Application

3.1 The Subcommittee reviewed an application from Alexion Pharmaceuticals for the listing of eculizumab (Soliris) on the Pharmaceutical Schedule for the treatment of paroxysmal nocturnal haemoglobinuria (PNH).

Recommendation

3.2 The Subcommittee **recommended** that the eculizumab be listed in the Pharmaceutical Schedule with a low priority subject to criteria limiting it to patients with paroxysmal nocturnal haemoglobinuria who:

- Have a clone size >50%, have systemic symptoms (for example severe abdominal pain, fatigue and shortness of breath) and there is evidence of active haemolysis; OR

- Have developed thrombosis despite adequate treatment (for example anticoagulation).

3.3 The Subcommittee considered that given the high cost of treatment, an advisory panel may be required to administer the treatment eligibility criteria.

3.4 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (iv) The clinical benefits and risks of pharmaceuticals and (vi) The budgetary impact of any changes to the Pharmaceutical Schedule.*

Discussion

3.5 The Subcommittee noted that this application had been reviewed by PTAC at its February 2012 meeting and has recommended that it be declined due to its high cost and the uncertainty around survival benefit with the treatment. The Subcommittee also noted that the supplier and Professor Peter Hillmen have provided feedback to some of the points raised by PTAC for review by the Subcommittee.

3.6 The Subcommittee noted that paroxysmal nocturnal haemoglobinuria (PNH) is an extremely rare disease characterised by complement-mediated haemolysis resulting in haemolytic anaemia, venous thromboembolisms and the associated symptoms. The Subcommittee noted that there is a range of treatments currently available but they are not very efficacious except for warfarin prophylaxis and supportive care with blood transfusion, iron and folate replacement.

3.7 The Subcommittee noted that the efficacy of eculizumab was investigated in 3 trials – the TRIUMPH study (Hillmen P et al. N Engl J Med 2006; 355(12): 1233-1243), the SHEPHERD study (Brodsky R et al. Blood 2008; 111(4): 1840-1847) and the Kelly et al study (Blood 2011; 117(25): 6786-92). The Subcommittee considered that the evidence was of medium strength and quality. The Subcommittee considered that the evidence available indicates that eculizumab is effective in reducing blood transfusion requirements and thrombosis rates.

3.8 The Subcommittee considered that the evidence of survival benefit with eculizumab was limited but it is likely to be associated with a survival benefit. The Subcommittee acknowledged that there were weaknesses associated with the Kelly et al study (Blood 2011; 117(25): 6786-92), namely that the lack of information regarding whether the treatment and control groups were matched adequately. The Subcommittee noted the response from Professor Peter Hillmen in regards to PTAC's comments on the French cohort study (de Latour et al. Blood 2008; 112: 3099) and considered that it was reasonable to conclude that the 92% 10-year survival rate estimate was probably too high given none of these patients (cohort diagnosed after 1996) were followed up for 10 years and only 18 of the 83 patients were followed up for 5 years. The Subcommittee also noted the response from Professor Peter Hillmen to PTAC's concerns regarding the 7-year study timeframe chosen in the Kelly et al study (Blood 2011; 117(25): 6786-92) and considered that his response was appropriate. The Subcommittee noted that previous studies have shown a median survival rate of 10 years for patients treated with best supportive care (Hillmen P et al. N Engl J Med. 1995;333(19):1253-1258) but considered that best supportive care including recommended warfarin anticoagulation is now better given that thrombosis is the largest risk factor in the patient population.

3.9 The Subcommittee noted that there would be an increased risk of serotype B meningococcal disease with eculizumab use and clinicians as well as patients would need to be vigilant of this increased risk, and establish prophylaxis and treatment algorithms.

3.10 The Subcommittee considered that there would be a small number of patients with a clone size of >50%, approximately 3 patients per million population. The Subcommittee considered that there is a high clinical need in this group of patients given the limited effective treatment alternatives. The Subcommittee considered that the patient group most likely to benefit from treatment with eculizumab would be patients who have developed thrombosis despite adequate treatment (anticoagulation) or those who have a clone size >50% with systemic symptoms (for example severe abdominal pain, fatigue and shortness of breath) and in whom there is evidence of active haemolysis.

3.11 The Subcommittee however noted the high drug cost for this treatment which resulted in its poor cost-effectiveness although evidence indicates it is an effective treatment. The Subcommittee noted that this is a significant issue especially given it is a long term treatment. The Subcommittee noted that this is the reason why the Canadian Agency for Drugs and Technologies in Health (CADTH) and Scottish Medicines Consortium did not recommend it for use within their jurisdictions.

3.12 The Subcommittee considered that there is no clinical reason why eculizumab should not be listed on the Pharmaceutical Schedule and recommended its listing with a low priority due to its extremely high cost. The Subcommittee also considered that if funded, patient compliance with treatment would need to be stressed.

February 2012 PTAC Minutes

18 Eculizumab for paroxysmal nocturnal haemoglobinuria

Application

18.1 The Committee reviewed an application from Alexion Pharmaceuticals for the listing of eculizumab (Soliris) on the Pharmaceutical Schedule for the treatment of paroxysmal nocturnal haemoglobinuria (PNH).

Recommendation

18.2 The Committee **recommended** that the application for eculizumab (Soliris) in paroxysmal nocturnal haemoglobinuria (PNH) be declined. The Committee also recommended that the application for eculizumab in PNH be referred to the Haematology Subcommittee for consideration.

18.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

18.4 The Committee noted that the evidence for eculizumab was mainly from observational studies with only one randomised controlled trial, the TRIUMPH study which was not powered to detect differences in either thrombosis rates or mortality. The TRIUMPH study (Hillmen et al. N Engl J Med. 2006; 355: 1233) was a double-blind, multi-centre, placebo-controlled trial involving 87 patients over a period of 6 months. The primary outcome of the trial was stabilisation of haemoglobin levels and transfusion requirements with a number of secondary outcome variables including the FACIT-Fatigue QOL score. The Committee considered that the findings from the study supports the claim that eculizumab does alleviate the haemolysis associated with PNH and the associated sequelae, thus improving symptoms and the quality of life for these patients. The Committee however noted that the study was not able to address the impact on life-threatening complications as only one thrombosis (in the placebo arm) occurred over the six month study period and there were no deaths.

18.5 The Committee considered that one of the major issues with eculizumab is its cost. The Committee considered that because the treatment with eculizumab does not alter the underlying defect of the disease, with the need for continued life-long therapy (unless spontaneous remission occurs in a minority of patients), it is crucial to understand the impact of eculizumab on mortality.

18.6 The Committee noted that the natural history studies on PNH have provided differing views on survival. The Committee noted that in Table 4 of the main submission, the supplier quotes a median survival ranging from 10 to 25 years. The Committee also noted a French cohort study (de Latour et al. Blood 2008; 112: 3099) of 460 PNH patients which showed a median survival of 22 years in the pre-eculizumab era with a 76.3% 10-year survival rate and more importantly a 92% 10-year survival rate in the 83 patients diagnosed after 1996. The Committee noted that this paper was not presented in Table 4 where survival rates were presented.

18.7 The Committee noted that the supplier put a significant amount of emphasis on the study by Kelly et al (Blood 2011; 117: 6786) from Leeds which attempted to address the issue of the natural history of PNH with a single centre review of 79 consecutive patients on eculizumab with a cohort of 30 patients

treated in the 7 years before the availability of eculizumab. The Committee noted that there were 3 deaths in the eculizumab arm compared to 5 deaths in the historical group. The Committee noted that the Kaplan-Meier survival curves showed a statistically significant difference (p=0.01) in the 5-year survival in the eculizumab arm versus the historical cohort, 95.5% (95% CI 87.6% - 98.5%) versus 66.8% (95%CI 41.4% - 85.1%). The Committee however considered that there was nearly an overlap in the two confidence intervals. The Committee also considered that it was unclear from the study why the period of 7 years was chosen. The Committee considered also that the comparison is lacking in many details with no description on the causes of death of the five individuals or even if the cohorts are matched in terms of age, sex or other co-morbidities. The Committee noted that an attempt to obtain more information from the primary author did not provide more confidence in the quality of the evidence.

18.8 The Committee noted the results from another publication from the same Leeds group, Hall et al (Blood 2003; 102: 3587) which looked at the natural history of PNH in the time preceding the availability of eculizumab. The Committee noted that the primary outcome of the paper was to investigate the role of warfarin as primary prophylaxis in preventing thrombosis in PNH but it also contained information on mortality. The Committee noted that the paper reviewed data on 163 of 179 consecutive patients with PNH clones investigated in the Leeds Laboratory prior to 2002. The Committee noted that of the 163 patients studied, with a median follow-up period of 6 years (range 0.2-38 years), there were 20 deaths (12.5%) of which 8 were attributable to PNH (4 attributed to liver thrombosis), 6 to aplasia and 5 probably unrelated to PNH with 1 unknown case. The Committee noted that the 5-year survival in this cohort is therefore greater than 87% which raises the suspicion that the Leeds group could have chosen the 7-year period for the Kelly et al (Blood 2011; 117: 6786) historical comparison to obtain a statistical significant result of reduced mortality with eculizumab. The Committee considered that if there was no survival advantage with eculizumab and only a reduction in blood transfusion requirements and fatigue, the cost per QALY for eculizumab would be very large. The Committee considered that the supplier estimation of an incremental gain of 32.5 life years for patients who receive eculizumab is too high.

18.9 The Committee noted that Hillmen et al (Blood 2007; 110: 4123) implies that the rate of thromboembolism is markedly reduced from 7.37 events/100 patient years prior to the usage of eculizumab to 1.07 events/100 patient years after commencing treatment. The Committee also noted that the authors concluded that “Considering that thrombosis has been demonstrated to cause the majority of deaths in PNH, it is reasonable to expect that eculizumab treatment, by decreasing the risk of thrombosis, may increase the life expectancy of these patients”. The Committee considered that although the data from the Hillmen et al study is quite compelling, the reduction in the rates of thromboembolism from before to after treatment may have an alternative explanation. The Committee considered that because thrombosis may lead to the diagnosis of the condition in the first place, it could be that thrombosis occurs earlier in the time course of the disease.

18.10 The Committee considered that there would be an increased risk of infections with eculizumab use – particularly meningococcal disease with 19 cases and 4 deaths resulting in a rate of 0.46/100 patient years of exposure (supplier submission). The Committee noted that because the serotype B meningococcal strain remains a significant New Zealand strain and cannot be prevented long term with currently available vaccines, not all meningococcal disease would be prevented with vaccination.

18.11 The Committee noted that the supplier’s estimates of PNH prevalence in New Zealand is possibly an overestimate but it is likely that uptake of eculizumab would be higher than the 35-50% range indicated by the supplier. The Committee considered that there was an unmet clinical need for PNH treatments. The patients most likely to benefit from treatment with eculizumab are those in need of frequent transfusions and those with a history of thrombosis. However, the Committee considered that given the uncertainty regarding mortality benefit, the effect of treatment with eculizumab is not in proportion to its current cost.

1.2 Description of Disease and Patient Population

Paroxysmal nocturnal haemoglobinuria (PNH) is an uncommon form of haemolytic anaemia and results from abnormal red blood cells, which are susceptible to complement-mediated haemolysis and unregulated activation of platelet and endothelial cells. It is this haemolysis (destruction of red blood cells) that is central to the pathophysiology of the clinical manifestations and the disease progression of PNH.

Between 10-45% of patients with PNH will have a clinical bone marrow deficiency. Bone marrow deficiency is recognised as an important co-morbidity in PNH as the clinical course of the disease can often be complicated by the co-existence of bone marrow dysfunctions. PNH clones are found in up to 70% of patients with acquired aplastic anaemia (AA) and 10-20% of patients with myelodysplastic syndromes (MDS).

Signs and Symptoms

The complications associated with the complement mediated haemolysis of the PNH red cells include life-threatening thrombosis, renal failure, pulmonary hypertension, anaemia, and smooth muscle spasm. Patients experience severe abdominal pain, fatigue, shortness of breath, dysphagia and erectile dysfunction.

Patients also experience acute exacerbations of haemolysis on a background of persistent elevated levels of haemolysis. The acute exacerbations can occur regularly or unpredictably and contribute to accelerating the progression or advancement of poor quality of life, morbidity and mortality.

Diagnosis

- Flow cytometry; uses monoclonal antibodies against proteins bound to GPI-APs to detect circulating cells in the patient's peripheral blood that are exhibiting deficient or absent expression of GPI-anchored proteins.

- Testing for intravascular haemolysis; lactate dehydrogenase levels.

Disease Course and Prognosis

PNH is a chronic disease with significant morbidity and mortality. However, a substantial number of patients live for extended periods, and spontaneous recovery may occur. Three reviews have examined the natural history of patients with this disorder.

- Hillmen et al. N Engl J Med. 1995;333(19):1253[1]

    - n=80 patients, median survival after the median age of onset of 42 years (range 16-75 years) for the disease was approximately 10 years, with 28% of patients surviving 25 years or more. Twelve of 35 patients who survived for longer than 10 years experienced a spontaneous recovery.

    - Approximately 60% of deaths were due to venous thrombosis or bleeding; one or more episodes of venous thrombosis occurred in almost 40% of the patients. There were no cases of acute leukaemia.

- Socié et al. Lancet. 1996;348 (9027):573[2]

    - n=220, median survival was 14.6 years with Kaplan-Meier survival estimates of 78%, 65%, and 48% at 5, 10, and 15 years after diagnosis, respectively. The median age of onset was 33 years (range 6-82 years). The eight-year rates of the major complications of PNH (pancytopenia, thrombosis, and myelodysplastic syndrome) were 15%, 28%, and 5% respectively. Adverse

prognostic factors included thrombosis, evolution to pancytopenia, myelodysplastic syndrome, or acute leukaemia, and age >55 years at onset of disease. Evidence of deficient haematopoiesis at disease onset, such as aplastic anaemia or thrombocytopenia, was a less powerful predictor of poor prognosis.

- Nishimura et al. Medicine (Baltimore). 2004;83(3):193[3]

    - This paper compared the clinical course of PNH patients in America and Japan. The onset of PNH among Japanese patients was more commonly in the setting of an aplastic or hypoplastic marrow than for the American patients. More strikingly, the prevalence of thrombosis was much greater among the American patients than among Japanese patients (38% versus 6%). The mean survival time for the Japanese patients was 32.1 years compared with 19.4 years for the American population, although the Kaplan-Meier survival curves were not different for the two groups. Note that the median age of onset was 45 years for the Japanese patients (range 10-86) and 30 years for the American population (range 4-80 years).

Historical studies until about 1996 show a median survival from diagnosis of between 10 and 16 years, whilst later studies using sensitive flow cytometry to identify both haemolytic and non-haemolytic patients report higher median survival times of 17.5 to 25 years.

A poor prognosis has been associated with a range of factors including: the occurrence of thrombosis as a complication; age at diagnosis; the need for additional treatment; renal insufficiency related to chronic haemosiderosis; liver failure; and the presence of thrombocytopenia leading to haemorrhage. Clone size has also been implicated as a prognostic factor.

1.3 Current Treatment in New Zealand

Other than stem cell transplantation, there is currently no known cure for PNH. The supplier indicates that patients receive best supportive care and do not have stem cell transplants given the high risk of mortality associated with stem cell transplantation. The mortality risk associated with stem cell transplant is considered too high for patients with PNH compared with current best supportive care.

Best supportive care

Best supportive care, as follows, should be considered the comparator to eculizumab. This includes:

- The replacement of iron and folic acid and the administration of red blood cell transfusions if clinically required.

- The administration of prednisone and/or androgenic hormones to suppress on going red cell destruction and/or the stimulation of haematopoiesis.

- Immunosuppression with antithymocyte serum which may be effective, particularly when signs of hematopoietic deficiency are present (e.g. granulocytopenia, thrombocytopenia, reticulocytopenia).

- High doses of erythropoietin or darbepoetin for some patients with diminished erythropoiesis, particularly if renal impairment is present. Recombinant granulocyte stimulating factor (G-CSF) has been used to increase the granulocyte count in granulocytopenic patients.

- Treatment with warfarin for the prevention of thrombosis. Patients with PNH are treated similarly to venous thrombosis occurring in other settings, with thrombolysis and anticoagulation; however, prednisone is also used since complement activation probably initiates thrombosis in patients with PNH. Anticoagulation is continued for an indefinite period of time in patients with recurrent episodes. Thrombosis in PNH appears to be related to the size of the abnormal platelet clone. In a retrospective study, patients with large PNH clones and no contraindication to anticoagulation were offered warfarin prophylaxis (Hall et al. 2003[4]). There were no thrombotic episodes in the 39 patients who received primary prophylaxis while 56% of patients not taking warfarin had a 10-year thrombosis rate of 36.5%.

Other treatments for PNH patients

Cyclosporine (for patients with marrow aplasia)

The role of cyclosporine for marrow aplasia in PNH remains to be determined in a larger number of patients. Cyclosporine does not appear to be beneficial in patients without aplasia in whom the hematologic and PNH characteristics are not changed (van Kamp et al. 1995[5]).

In Stoppa et al. 1996[6], cyclosporine was tried as an alternative to haemopoietic cell transplantation for aplastic anaemia in a small number of patients. A complete response was noted in two patients after 6 and 24 months, and a partial response in the third after 12 months. The PNH clone and haemolysis persisted. The disease relapsed in two patients in whom cyclosporine was withdrawn.

Haemopoietic Cell Transplantation (HCT)

There is a high risk of mortality associated with HCT for patients with PNH. The Peffault de Latour[7] trial states that HCT "is probably not a suitable treatment option for life-threatening thromboembolism in paroxysmal nocturnal hemoglobinuria". The evidence shows that five year survival rates are lower in patients who receive transplants compared with those that have not. However, severe haematopoietic dysfunction leading to marked cytopenias can be successfully treated with HCT. In a registry study involving 57 patients, it was indicated that bone marrow transplantation can restore normal bone marrow function in about 50% of PNH patients (Saso et al. 1999[8]).

Asymptomatic patients, especially those with a PNH clone <10%, or those with only mild symptoms should not be treated with eculizumab. PNH clone size should be determined every 6 to 12 months in order to monitor for disease progression prior to the onset of symptoms.

1.4 Pharmaceutical Under Assessment

Eculizumab aims to inhibit the complement-mediated intravascular haemolysis, the central morbidity in PNH, by inhibiting and preventing terminal complement activation. Eculizumab is administered by infusion, and once it is in the blood stream, eculizumab binds to the complement protein C5 with high affinity and specificity. Binding of eculizumab to C5 prevents the cleavage of C5 into C5a and C5b and in doing so, inhibits a series of binding steps required to produce the lytic membrane attack complex (MAC) and the proinflammatory molecule C5a. MAC formation is normally blocked by the red blood cell-bound natural complement inhibitor CD59. However, CD59 is deficient or absent in PNH red blood cells, so MAC formation is unregulated and the unprotected cells are susceptible to lysis by the activated terminal complement system. By preventing MAC formation, eculizumab replaces the missing protective function of CD59 and stops the insertion of pores or channels through the unprotected PNH red cell membranes; thereby saving the PNH red cells from complement-mediated lysis.

However, evidence shows that eculizumab is not effective in all patients with PNH, and some patients who receive eculizumab may require on-going blood transfusions for their haemolysis.

Registered indication, dosing and administration

Eculizumab is registered in New Zealand and indicated for the treatment of patients with PNH to reduce haemolysis.

Patients must be administered a meningococcal vaccine at least two weeks prior to initiation of eculizumab therapy and revaccinated according to current medical guidelines for vaccine use.

The recommended dosage for eculizumab is:

- 600 mg every 7 days for the first 4 weeks, followed by
- 900 mg for the fifth dose 7 days later, then
- 900 mg every 14 days thereafter.

2 Clinical Effectiveness Review

2.1 Literature Search Strategy

A literature search was conducted by PHARMAC staff for randomised controlled trials, review articles, meta-analyses, and guidelines on eculizumab for PNH. The PubMed database was used and search terms included “eculizumab” and “Hemoglobinuria”, as well as “eculizumab” in the Cochrane Library in December 2011. Further more recent searches have been undertaken to check for new evidence in March 2013.

All relevant citations were assessed for inclusion in the clinical effectiveness review. The search was supplemented by material provided by the supplier in its submission and references from key articles from searches. The following websites were also searched:

- National Institute for Health and Care Excellence (UK): http://www.nice.org.uk/
- Canadian Agency for Drugs and Technology in Health: http://www.cadth.ca/
- Scottish Medicines Consortium: http://www.scottishmedicines.org.uk/
- Australian Pharmaceutical Benefits Scheme: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/public-summary-documents

Independent expert clinical advice was provided by PTAC and the Haematology Subcommittee of PTAC.

2.2 Details of Key Clinical Evidence

The table below summarises the available clinical evidence for eculizumab in PNH:

Study	Study Phase/ Design	Duration/Status	
Hillmen P, et al. N Engl J Med 2006;355 (12):1233-1243[9] TRIUMPH study	Phase III, double-blind placebo, RCT	26 weeks, complete	• Primary endpoints in the study were stabilization of haemoglobin levels and the number of units of red cells transfused. • N=87, placebo vs eculizumab was given at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900-mg dose and then 900 mg every other week through week 26. • Stabilisation of haemoglobin levels in the absence of transfusions was achieved in 49% (21 of 43) of the patients assigned to eculizumab and none (0 of 44) of those assigned to placebo (P<0.001). During the study, a median of 0 units of packed red cells was administered in the eculizumab group, as compared with 10 units in the placebo group (P<0.001). Eculizumab reduced intravascular haemolysis, as shown by the 85.8% lower median area under the curve for lactate dehydrogenase plotted against time (in days) in the eculizumab group, as compared with the placebo group (58,587 vs. 411,822 U per litre; P<0.001).
Hillmen P, et al. N Engl J Med 2004;350:552-559[10] PILOT study	Phase II, open label	12 weeks, complete	• N=11 received eculizumab 600mg every week for 4 weeks, followed one week later by a 900 mg dose and then by 900 mg every 2 weeks through week 12 • Mean lactate dehydrogenase levels decreased from 3111 IU per litre before treatment to 594 IU per litre during treatment (P=0.002). The mean percentage of PNH type III erythrocytes increased from 36.7 percent of the total erythrocyte population to 59.2 percent (P=0.005). The mean and median transfusion rates decreased from 2.1 and 1.8 units per patient per month to 0.6 and 0.0 units per patient per month, respectively (P=0.003 for the comparison of the median rates). Episodes of haemoglobinuria were reduced by 96 percent (P<0.001), and measurements of the quality of life improved significantly.

Study	Study Phase/ Design	Duration/Status	
Hill A, et al. Blood 2005;106:2559-65[11]; Extended Pilot Study	Phase II, open label	52 weeks, complete	• N=11, eculizumab at 900 mg every 12 to 14 days. • Reduction in haemolysis was maintained throughout the study, with a decrease in LDH levels from 3110.7 IU/L before treatment to 622.4 IU/L (P =.002). The proportion of PNH type III RBCs increased from 36.7% at baseline to 58.4% (P = .005). The paroxysm rate of days with gross evidence of haemoglobinuria per patient each month decreased from 3.0 during screening to 0.2 (P < .001). The median transfusion rate decreased from 1.8 U per patient each month before eculizumab treatment to 0.3 U per patient each month (P =.001) during treatment. Statistically significant improvements in quality-of-life measures were also maintained during the extension study. Eculizumab continued to be safe and well tolerated, and all patients completed the study.
Brodsky R, et al. Blood 2008;111(4):1840-1847[12] SHEPHERD study	Phase III, open-label	52 weeks, complete	• Primary endpoint for efficacy was haemolysis as assessed by LDH area under the curve, and for safety included adverse events, electrocardiogram data and vital signs. • N=97, eculizumab was administered by intravenous infusion at 600 mg every 7 +/- 2 days for 4 weeks; 900 mg 7 +/- 2 days later; followed by 900 mg every 14 +/- 2 days for a total treatment period of 52 weeks. • Patients treated with eculizumab responded with an 87% reduction in haemolysis, as measured by lactate dehydrogenase levels (P < .001). Baseline fatigue scores in the FACIT-Fatigue instrument improved by 12.2 +/-1.1 points (P < .001)(range between 0 and 52, where the higher the score the higher the quality of life). Eculizumab treatment led to an improvement in anaemia. The increase in haemoglobin level occurred despite a reduction in transfusion requirements from a median of 8.0 units of packed red cells per patient before treatment to 0.0 units per patient during the study (P < .001). Overall, transfusions were reduced 52% from a mean of 12.3 to 5.9 units of packed red cells per patient. Forty-nine patients (51%) achieved transfusion independence for the entire 52-week period.

Study	Study Phase/ Design	Duration/Status	
Hillmen P, et al. Blood 2007;110(12):4123-8;[13] Extended pilot, TRIUMPH and SHEPHERD	Phase III, open-label	104 weeks, complete	• N=195, Clinical trial participants included all patients in the 3 eculizumab PNH clinical studies, which recruited patients between 2002 and 2005 • The thromboembolism (TE) event rate with eculizumab treatment was 1.07 events/100 patient-years compared with 7.37 events/100 patient-years (P < .001) prior to eculizumab treatment (relative reduction, 85%; absolute reduction, 6.3 TE events/100 patient-years).With equalization of the duration of exposure before and during treatment for each patient, TE events were reduced from 39 events before eculizumab to 3 events during eculizumab (P < .001). The TE event rate in antithrombotic-treated patients (n = 103) was reduced from 10.61 to 0.62 events/100 patient-years with eculizumab treatment (P < .001).
Kanakura Y, et al. Int J Hematol 2011;93:36-46[14] AEGIS	Phase II, open-label	12 weeks, complete	• Primary endpoint to reduce intravascular haemolysis with high statistical significance • N=29. The pivotal open-label, 12-week phase II registration study (AEGIS) was designed to evaluate the efficacy and safety of eculizumab in Japanese patients with PNH. • Twenty-seven of the 29 patients responded to eculizumab treatment, resulting in an 87% reduction in haemolysis (P<0.0001) and subsequent improvement in anaemia (P = 0.0003) despite reduction in transfusion requirements (P = 0.006). Fatigue and dyspnoea significantly improved within 1–2 weeks of eculizumab treatment and the improvement was independent of changes in haemoglobin. Chronic kidney disease (CKD) was common (66%) and eculizumab treatment improved CKD in 41% of patients at 12 weeks (P<0.001). Elevated thrombotic risk was evident in Japanese PNH patients and eculizumab treatment normalized D-dimer levels in 45% of patients with elevated D-dimers at baseline (P<0.001).

Study	Study Phase/ Design	Duration/Status	
Kelly RJ, et al. Blood 2011; 117(25):6786-92.[15]	Phase IV	182 weeks, complete	• N=79 • The survival of the 79 patients treated with eculizumab was not different to an age and sex matched normal control population (p=0.46) but was significantly better than 30 similar patients with PNH managed in the 7 years before eculizumab (Hazard Ratio 0.21, 95% CIs 0.05-0.88, p=0.030). The 5 year survival rate was 66.8% (95% CI 41.4%-85.1%) for these 30 patients compared with 95.5% (95% CI 87.6%-98.5%) for those who received eculizumab. Three of the 79 (3.8%) patients on eculizumab, all over 50 years old, died from causes unrelated to PNH. Twenty-one of the 79 patients (27%) had a thrombosis prior to starting eculizumab (5.6 events per 100 patient years) compared with 2 thrombotic episodes on eculizumab (0.8 events per 100 patient years; p<0.001). Twenty-one patients with no prior history of thrombosis discontinued warfarin after starting eculizumab with no thrombotic sequelae. Forty of 61 (66%) patients on treatment for over 12 months achieved transfusion independence on eculizumab. The mean transfusion requirement reduced by 74% falling from 19.3 units in the 12 month period immediately prior to commencing eculizumab to 5.0 units in the most recent 12 months on eculizumab in these 61 patients (p<0.001).

2.3 Discussion of Results

Hillmen et al 2006[9] is the pivotal trial being a randomised, phase III double blinded clinical trial. The other trials for eculizumab are of relatively low quality, i.e. they are open-label and not randomised controlled trials. The results of the clinical trials show that eculizumab has clinical benefits for patients with PNH. Reductions in haemolysis, thrombotic events, and renal complications as well as reductions in blood and platelet transfusions will increase the quality of life for patients.

Kelly et al 2011[15] reports differences in survival between patients who received eculizumab and those who received best supportive care. Although PTAC (in March 2013) did not agree that patients who receive eculizumab would have a 'normal' life expectancy, they did consider there would be an increase in survival compared with best supportive care.

2.4 Safety

Meningococcal infection is the most serious adverse event for patients who receive eculizumab. In the Hillmen et al 2006 trial there were three cases of Neisseria meningitides in patients who received eculizumab (3/43, 7%). Two of these patients had been vaccinated against meningitis, but it is not stated how long they had been vaccinated before infection. No patients died from meningitis. However, as a result all patients to be treated with eculizumab are required to be vaccinated at least two weeks before starting treatment as stated in the Medsafe data sheet[16].

3 International Recommendations

NHS Specialised Services in England

Eculizumab has been funded for PNH by the NHS Specialised Services in England since April 2009. However, there is no discussion regarding the cost-effectiveness of eculizumab for PNH[17].

Scottish Medicines Consortium (SMC)

Eculizumab for PNH has not been recommended by the SMC as of July 2011. The manufacturer did not provide any cost-effectiveness information for eculizumab. After an independent health economic review the cost-effectiveness of eculizumab was not demonstrated. They estimate the annual cost of eculizumab per patient to be £252,000 (NZ ~$500,000)[18]. However as SMC advice is not binding, Health Boards in Scotland are able to offer patients eculizumab. It is also possible that patients may move or travel to England to receive treatment if it is not available in Scotland.

Canadian Expert Drug Advisory Committee (CEDAC)

CEDAC recommended that eculizumab should not be listed at the price submitted by the manufacturer in February 2010. They note the cost of eculizumab is exceptionally high (more than CA$ 500,000 per patient per year). They estimate a cost per QALY of CA$2.4 million (approximately NZ$2.8 million per QALY) for eculizumab with best supportive care compared with best supportive care alone based on 26 week trial data. They note that quality of life improvement over a lifetime may not have been fully captured. After taking into account potential lifetime quality of life gains they note that the cost per QALY will not be below CA $500,000[19]. Note, that according to the supplier, eculizumab has been available in Canada since July 2011.

Australia

In July 2008 the Pharmaceutical Benefits Advisory Committee in Australia reviewed an application for eculizumab for patients with PNH. They state that the cost-effectiveness ratio was estimated to be greater than AU$200,000 per additional death avoided over a two year period[20]; no CUA result was discussed.

Subsequently eculizumab was made available in Australia in 2010 outside of the Pharmaceutical Benefits Scheme under the Life Saving Drug Program (LSDP) (see details at http://www.health.gov.au/lsdp). The LSDP subsidises access “for eligible patients, to expensive life saving drugs for very rare life-threatening conditions”. To be available on the LSDP, the pharmaceutical must usually be accepted by the Pharmaceutical Benefits Advisory Committee (PBAC) as clinically necessary and effective.

4 Economic Analysis

4.1 Scope of Analysis

Decision Problem and Perspective

A preliminary cost-utility analysis was undertaken to estimate the QALYs gained per $1 million invested in eculizumab for patients with paroxysmal nocturnal haemoglobinuria (PNH). The supplier provided costing information for the analysis that has been used for our preliminary assessment. All costs and benefits were discounted at 3.5% as per the Prescription for Pharmacoeconomic Analysis (PFPA)[21].

This analysis was conducted from the perspective of the funder, with regards to PHARMAC's decision criteria. The levels of analysis are described in the PFPA.

Target Population

The target population for this analysis was defined as patients with PNH who met the following criteria proposed by PTAC:

- Have a clone size >50%, have systemic symptoms (for example severe abdominal pain, fatigue and shortness of breath) and there is evidence of active haemolysis; OR
- Have developed thrombosis despite adequate treatment (for example anticoagulation).

Comparator

The comparator used in the analysis is current treatment; usually warfarin, as well as blood and platelet transfusions. There are currently no funded treatments specifically for patients with PNH. Some treatments i.e. anticoagulants are used to prevent thrombotic events which occur in patients with PNH.

Bone marrow transplant has not been included as a comparator at this stage as this is not typically current treatment in New Zealand due to the high risk of mortality associated with the transplant, as stated by PTAC in March 2013.

4.2 Economic Model

An economic model was constructed to examine the cost-effectiveness of eculizumab for patients with PNH. This modelling includes sensitivity analysis which tests key inputs including assumptions regarding quality and quantity of life gains from treatment with eculizumab. The gains in life expectancy are uncertain, however, based on advice from PTAC in March 2013 the analysis tests a plausible range to inform the result.

Time Horizon

The time-horizon of the cost-utility analysis (CUA) is a lifetime horizon. Advice from PTAC states it is unlikely that patients will achieve normal life expectancy. All costs and benefits were discounted at 3.5%.

Model Structure

The model included health states where patients received either current treatment or eculizumab plus best supportive care as lifelong treatment. Patients accrue quality adjusted life years and costs associated with each treatment every year.

Key Assumptions and Inputs

Relatively optimistic assumptions have been used in this preliminary assessment. This means that the gains and costs associated with treatment are likely to need further assessment if a new commercial arrangement with the supplier is reached.

The following inputs are used in the base case and then varied/tested in sensitivity analysis:

- Response to treatment is assumed to be 100%, with no adverse events or discontinuation due to adverse events modelled;
- 900 mg eculizumab per fortnight after induction dosing as described in section 1.4 (via infusion);
- Treatment is lifelong;
- Average age of patients first receiving eculizumab is 35 years;
- Average age at death of best supportive care is 55 years;
- Average age at death with eculizumab and best supportive care is 60 years; and
- Cost of eculizumab (per 300 mg vial) of [redacted] (~$27,000 per cycle or $670,000 per year per patient).

These treatment assumptions may overstate the effectiveness of treatment and its net clinical benefits.

Transformation and Extrapolations

There is uncertainty regarding the life expectancy gains of patients who receive treatment with eculizumab. The supplier has estimated that a patient treated with eculizumab would have a 'normal' life expectancy (based on the Kelly et al 2011[15] trial). PTAC stated in paragraph 1.14 of the March 2013 PTAC minute there would likely be an increase in life expectancy compared with current treatment, although the amount was uncertain. Therefore, we used a notional relative risk of 1.25 (i.e. a quarter improvement in life expectancy). This estimates that the average age of death for a patient with PNH on current treatment is 55 years and for a patient receiving eculizumab is 60 years; the average age patient's first receiving eculizumab is assumed to be 35. This assumption is tested in the sensitivity analysis.

4.3 Health-Related Quality of Life

There is uncertainty regarding quality of life scores and patients' health states. At present the analysis optimistically assumes that patients who receive eculizumab have a quality of life score of approximately 1.0 (full health) for the remainder of their life.

In this preliminary assessment we have assumed that patients who receive current treatment have a quality of life score of approximately 0.535 for the remainder of their life. The quality of life score was based on expert clinical opinion derived using the NZ EQ-5D. This assumption may overstate the loss in quality of life for patients who receive current treatment.

The quality of life score of 0.535 takes into account that a patient with PNH will have some problems in walking about, no problems with self-care, some problems performing usual activities, moderate pain or discomfort and be moderately anxious or depressed (NZ EQ-5D score 2,1,2,2,2).

4.4 Costs

The cost of eculizumab was estimated to be approximately $685,000 per patient in the first year using a dose of 600 mg weekly for four weeks, 900 mg in week 5, then 900 mg fortnightly thereafter. Subsequent treatment costs approximately $670,000 per patient per year. This is based on the proposed price of [redacted] per 300 mg vial. Patients continue to receive eculizumab whilst they receive benefit from the treatment. This preliminary analysis assumes that all patients adhere to the regimen and they receive the same level of benefit from on-going treatment for the rest of their life.

This preliminary assessment does not include the cost of blood or platelet transfusions or the cost of the intravenous infusion of eculizumab. These costs are relatively small in comparison to the current cost of eculizumab (approximately 1% of all costs). The cost of anticoagulation therapy is not included in analysis as usage is assumed to be the same in both treatment arms.

However, we note the supplier included estimated cost offsets of between $5,000 and $10,000 per year, based on reduced blood transfusions, reduced rate of thrombotic events and reduction in renal failure events. The cost of intravenous infusion for eculizumab is estimated to be approximately $15,000 per year.

4.5 Results of Economic Analysis

The CUA range is between 0.4 – 0.9 QALYs per $1 million invested ($1,100,000- $2,500,000 per QALY). This is based on incremental gains of 9.2 QALYs with incremental costs of $11.4 million over the 25 year time horizon in the model. Note that an incremental 6.8 QALYs accrue from increased quality of life and 2.4 QALYs from extended life.

This analysis models the cost-effectiveness for patients with PNH who meet the criteria outlined by PTAC and the Haematology Subcommittee. If the analysis was widened to include all patients with PNH who could benefit from eculizumab then the average QALY gain per patient would be lower.

4.6 Sensitivity Analysis

<u>One-way Sensitivity Analysis</u>

Several plausible scenarios have been tested regarding the assumptions in the economic model. The results are shown in the table below:

Variable	Base case	Tested range	Cost per QALY	QALYs per $1m
Base case			$1,240,000	0.8
Utility with standard care	0.535	0.45	$1,100,000	0.9
		0.65	$1,520,000	0.7
Utility with eculizumab	1	0.7	$2,810,000	0.4
		0.8	$1,980,000	0.5
Life expectancy from age 35 with eculizumab treatment	25 years (5years more than best supportive care)	20 years (same as best supportive care)	$1,440,000	0.7
		40 years (20 years more than best supportive care)	$1,080,000	0.9
Years until price reduction of 95% due to bio-similar entry	Not taken into account	15 years	$940,000	1.1
		25 years	$1,260,000	0.8
Price per 300 mg vial of	[redacted]	[redacted] (50% off)*	$620,000	1.6

Variable	Base case	Tested range	Cost per QALY	QALYs per $1m
eculizumab		[redacted] (75% off)*	$310,000	3.2
		[redacted] (90% off)*	$125,000	8.0
Discount rate	3.50%	0%	$1,170,000	0.9
		5%	$1,270,000	0.8

*Note: further assessment is likely to occur if we receive a new commercial offer from the supplier and this may make the proposal less cost-effective than stated here.

The model is most sensitive to the price of eculizumab; a 90% price reduction results in the most cost-effective result of 8 QALYs per $1 million invested ($125,000 per QALY). The analysis is less sensitive to other variables with CUA results ranging from 0.4 - 1.1 QALYs per $1 million invested ($900,000-$2,500,000 per QALY). The greater the life expectancy gain from eculizumab treatment the more cost-effective the treatment is when compared with current treatment.

The availability and inclusion of a bio-similar pharmaceutical in the future would make the proposal look more cost-effective. The sooner a bio-similar was available the more cost-effective the proposal would be. However, there is uncertainty around when a bio-similar version of eculizumab would be available and how much it would cost.

Sensitivity analysis also shows that the discount rate (3.5% for both benefits and costs) does not appreciably alter the CUA result; this is because both benefits and costs accrue at the same rate over time.

Two-way Sensitivity Analysis

Several two way sensitivity analyses have been assessed. The table below shows the QALYs gained per $1 million invested when changing the utility score for patients who receive eculizumab and the price per 300 mg vial of eculizumab:

	Utility on eculizumab		
Price per 300 mg vial of eculizumab	**1.0**	**0.8**	**0.7**
[redacted] **Base case**	0.8	0.5	0.4
[redacted] **50% off**	1.6	1.0	0.7
[redacted] **75% off**	3.2	2.0	1.4

The higher the utility score and lower the price per vial of eculizumab the better the CUA result (i.e. 3.2 QALYs per $1 million invested).

The table below shows the QALYs gained per $1 million invested when changing the utility score for patients who receive current treatment and the price per 300 mg vial of eculizumab:

Price per 300 mg vial of eculizumab	Utility on current treatment		
	0.45	0.535	0.65
[redacted] Base case	0.9	0.8	0.7
[redacted] 50% off	1.8	1.6	1.3
[redacted] 75% off	3.7	3.2	2.6

The results from this two way analysis show that the CUA is extremely sensitive to the price per vial of eculizumab and the utility score with current treatment has a relatively small impact. Even with a 50% price reduction for eculizumab the effect on the CUA result by amending the utility score is small.

The table below shows the QALYs gained per $1 million invested when changing the potential life expectancy for patients who receive eculizumab at age 35 and the price per 300 mg vial of eculizumab:

Price per 300 mg vial of eculizumab	Potential life expectancy with eculizumab		
	55 years	60 years	75 years
[redacted] Base case	0.7	0.8	0.9
[redacted] 50% off	1.4	1.6	1.9
[redacted] 75% off	2.8	3.2	3.7

The longer the potential life expectancy with eculizumab the more cost-effective eculizumab is. However, in this scenario, the CUA result is much more sensitive to the price per 300 mg vial of eculizumab.

5 Discussion

The main benefits of treating PNH patients with eculizumab include a reduction in haemolysis, thrombotic events and renal complications as well as a small reduction in blood transfusions. Expert clinical advice to PHARMAC also noted that there is likely to be an increase in life expectancy beyond that with current treatment, but not to full life expectancy. Our advice also noted that eculizumab is not effective in all patients with PNH, many who may continue to receive on-going blood transfusions. It is unclear as to how much gain in life expectancy patients would receive from eculizumab. Even with the relatively optimistic benefits that have been attributed to eculizumab in this preliminary CUA, a significant price reduction is likely to be required before this proposal becomes relatively cost-effective compared with other proposals.

Any further assessment is likely to include:

- additional health states showing the deterioration over time in patients with PNH;
- greater clarity regarding the quality of life of these patients;
- impact of adverse effects of eculizumab;
- the proportion of patients that are likely to receive benefit from eculizumab;
- possible long-term safety impacts of receiving eculizumab; and
- costs and savings associated with blood transfusions and the infusion cost of eculizumab that are not currently included in the model.

This analysis models the cost-effectiveness for patients with PNH who meet the criteria outlined by PTAC and the Haematology Subcommittee. If the analysis was widened to include all patients with PNH then the average QALY gain per patient would be lower.

References

[1] Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995 Nov 9;333(19):1253-8.

[2] Socié G, Mary JY, de Gramont A, Rio B, Leporrier M, Rose C, Heudier P, Rochant H, Cahn JY, Gluckman E. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology. Lancet. 1996 Aug 31;348(9027):573-7.

[3] Nishimura J, Kanakura Y, Ware RE, Shichishima T, Nakakuma H, Ninomiya H, Decastro CM, Hall S, Kanamaru A, Sullivan KM, Mizoguchi H, Omine M, Kinoshita T, Rosse WF. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. Medicine (Baltimore). 2004 May;83(3):193-207.

[4] Hall C, Richards S, Hillmen P. Primary prophylaxis with warfarin prevents thrombosis in paroxysmal nocturnal hemoglobinuria (PNH). Blood. 2003 Nov 15;102(10):3587-91

[5] van Kamp H, van Imhoff GW, de Wolf JT, Smit JW, Halie MR, Vellenga E. The effect of cyclosporine on haematological parameters in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 1995 Jan;89(1):79-82

[6] Stoppa AM, Vey N, Sainty D, Arnoulet C, Camerlo J, Cappiello MA, Gastaut JA, Maraninchi D. Correction of aplastic anaemia complicating paroxysmal nocturnal haemoglobinuria: absence of eradication of the PNH clone and dependence of response on cyclosporin A administration. Br J Haematol. 1996 Apr;93(1):42-4.

[7] Peffault de Latour R, Schrezenmeier H, Bacigalupo A, Blaise D, de Souza CA,Vigouroux S, Willemze R, Terriou L, Tichelli A, Mohty M, de Guibert S, Marsh JC, Passweg J, Yves Mary J, Socié G. Allogeneic stem cell transplantation inparoxysmal nocturnal hemoglobinuria. Haematologica. 2012 Nov;97(11):1666-73. doi:10.3324/haematol.2012.062828. Epub 2012 Jun 11.

[8] Saso R, Marsh J, Cevreska L, Szer J, Gale RP, Rowlings PA, Passweg JR, Nugent ML, Luzzatto L, Horowitz MM, Gordon-Smith EC. Bone marrow transplants for paroxysmal nocturnal haemoglobinuria. Br J Haematol. 1999 Feb;104(2):392-6.

[9] Hillmen P, Young NS, Schubert J, Brodsky RA, Socié G, Muus P, Röth A, Szer J, Elebute MO, Nakamura R, Browne P, Risitano AM, Hill A, Schrezenmeier H, Fu CL, Maciejewski J, Rollins SA, Mojcik CF, Rother RP, Luzzatto L. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006 Sep 21;355(12):1233-43.

[10] Hillmen P, Hall C, Marsh JC, Elebute M, Bombara MP, Petro BE, Cullen MJ, Richards SJ, Rollins SA, Mojcik CF, Rother RP. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2004 Feb 5;350(6):552-9.

[11] Hill A, Hillmen P, Richards SJ, Elebute D, Marsh JC, Chan J, Mojcik CF, Rother RP. Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria. Blood. 2005 Oct 1;106(7):2559-65. Epub 2005 Jun 28.

[12] Brodsky RA, Young NS, Antonioli E, Risitano AM, Schrezenmeier H, Schubert J, Gaya A, Coyle L, de Castro C, Fu CL, Maciejewski JP, Bessler M, Kroon HA, Rother RP, Hillmen P. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008 Feb 15;111(4):1840-7. Epub 2007 Nov 30.

[13] Hillmen P, Muus P, Dührsen U, Risitano AM, Schubert J, Luzzatto L, Schrezenmeier H, Szer J, Brodsky RA, Hill A, Socié G, Bessler M, Rollins SA, Bell L, Rother RP, Young NS. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. Blood. 2007 Dec 1;110(12):4123-8. Epub 2007 Aug 16.

[14] Kanakura Y, Ohyashiki K, Shichishima T, Okamoto S, Ando K, Ninomiya H, Kawaguchi T, Nakao S, Nakakuma H, Nishimura J, Kinoshita T, Bedrosian CL, Valentine ME, Khursigara G, Ozawa K, Omine M. Safety and efficacy of the terminal complement inhibitor eculizumab in Japanese patients with paroxysmal nocturnal hemoglobinuria: the AEGIS clinical trial. Int J Hematol. 2011 Jan;93(1):36-46. doi: 10.1007/s12185-010-0748-9. Epub 2011 Jan 12.

[15] Kelly RJ, Hill A, Arnold LM, Brooksbank GL, Richards SJ, Cullen M, Mitchell LD, Cohen DR, Gregory WM, Hillmen P. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood. 2011 Jun 23;117(25):6786-92. doi: 10.1182/blood-2011-02-333997. Epub 2011 Apr 1.

[16] Medsafe data sheet for eculizumab http://www.medsafe.govt.nz/profs/Datasheet/s/solirininf.pdf

[17] NHS Specialised Services, UK http://www.specialisedservices.nhs.uk/service/paroxysmal-noctural-haemoglobunuria

[18] Scottish Medicines Consortium. Recommendation for eculizumab in patients with PNH. July 2011 http://scottishmedicines.org.uk/files//advice/eculizumab_Soliris_FINAL_AMENDED_11_July_2011_for_website.pdf

[19] Canadian Expert Drug Advisory Committee (CEDEC). Final recommendation for eculizumab in patients with PNH. February 2010,

http://www.cadth.ca/media/cdr/complete/cdr_complete_Soliris_February_18_2010.pdf

[20] Pharmaceuticals Benefits Advisory Committee (PBAC) recommendation, 2008. http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-eculizumab-july08

[21] Prescription For Pharmacoeconomic Analysis; Methods for cost-utility analysis Version 2.1 - 2012 http://www.pharmac.health.nz/ckeditor_assets/attachments/5/pfpafinal.pdf