PTAC & Haematology Subcommittee minutes regarding eculizumab for paroxysmal nocturnal haemaglobinuria (PNH)

PTAC (teleconference) 18 March 2013:

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.

PTAC 14 & 15 February 2013

4.3 Haematology Subcommittee Minutes – 6 August 2012

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.

Haematology Subcommittee 6 August 2012

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.

PTAC 16 & 17 February 2012

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.