PUBLIC SUMMARY DOCUMENT
Product: Eculizumab, solution concentrate for I.V. infusion, 300 mg in 30 mL, Soliris®
Sponsor: Alexion Pharmaceuticals, Inc
Date of PBAC Consideration: July 2008

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) PBS listing or inclusion on the Life Saving Drugs Program for treatment of paroxysmal nocturnal haemoglobinuria (PNH).

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Eculizumab was TGA registered on 3 March 2008 for the treatment of patients with paroxysmal nocturnal haemoglobinuria to reduce haemolysis.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drug) Private hospital authority required
Treatment of patients with paroxysmal nocturnal haemoglobinuria to reduce haemolysis.

OR
Inclusion on the Life Saving Drugs Program (LSDP) for treatment of paroxysmal nocturnal haemoglobinuria (PNH), if rejected for PBS listing.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Paroxysmal nocturnal haemoglobinuria (PNH) is an extremely rare and life threatening disease that is associated with a clonal disorder of the haemopoietic stem cell. The condition is characterised by chronic haemolysis, which is responsible for most of the clinical manifestations of the disease, including severe anaemia, life threatening thromboses, kidney damage and failure and disabling fatigue. PNH is most often a disease of young adults with the median onset in the early to mid thirties.

Currently no therapy exists to treat PNH. Therapeutic management of PNH treats disease symptoms only and is mainly supportive in nature.

Eculizumab would provide a treatment for patients with paroxysmal nocturnal haemoglobinuria to reduce haemolysis. However, it is not curative for the underlying disease.

6. Comparator

The submission nominated supportive care as the main comparator. The PBAC considered this was appropriate.

7. Clinical Trials

The submission presented the following trials in support of the requested listing:

- Primary evidence: one 26-week Phase III randomised trial (C04-001 TRIUMPH) comparing eculizumab with placebo in transfusion-dependent patients with PNH
- Supportive evidence: two open-label uncontrolled single-arm studies (52-week Phase III C04-002 SHEPHERD study and 12-week Phase II C02-001 PILOT) and their extension studies.

The trials published at the time of submission are as follows:

Trial/First author	Protocol title/ Publication title	Publication citation
Randomised trial		
C04-001 (TRIUMPH) Hillmen P, et al.	The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Haemoglobinuria.	N Engl J Med 2006; 355 (12):1233-1243.
Supportive non-randomised trials		
C04-002 (SHEPHERD) Brodsky R, et al.	Multicentre Phase 3 Study of the Complement Inhibitor Eculizumab for the Treatment of Patients with Paroxysmal Nocturnal Haemoglobinuria.	Blood 2008; 111 (4):1840-1847.
C02-001 (Pilot Study) & 2 extension studies Hillmen P ,et al	Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria.	N Engl J Med 2004, 350:552-559.
Hill A, et al.	Sustained response and long-term safety of eculizumab in paroxysmal nocturnal haemoglobinuria.	Blood 2005; 106:2559-65.
E05-001 (Phase 3 Common Extension Trial) Hillmen P , et al.	Effect of the Complement Inhibitor Eculizumab on Thromboembolism in Patients with Paroxysmal Nocturnal Haemoglobinuria.	Blood 2007; 110 (12):4123-8.

8. Results of Trials

The submission stated that eculizumab significantly reduced intravascular haemolysis, as measured by serum lactate dehydrogenase (LDH), and the transfusion requirements of patients with PNH – about half of the patients who received eculizumab therapy did not require transfusions in the 26-week TRIUMPH and the 52-week SHEPHERD. Almost 49% of patients in the TRIUMPH trial achieved haemoglobin (Hb) stabilisation.

Only 15 (35%) of the 43 eculizumab patients in the TRIUMPH trial achieved normalised LDH. However, compared to placebo, where none of the patients achieved LDH normalisation, this result was statistically significant ($p < 0.001$). The evidence of sustained reduction of LDH was limited to 21 patients who received 2.5 years of eculizumab therapy and 10 patients who received 4.5 years of treatment.

The results of TRIUMPH, SHEPHERD and E05-011 trials are summarised as below:

	Eculizumab		Placebo		p-value
Change in LDH from baseline (IU/L): mean (median)					
TRIUMPH (26 weeks)	−1850 (−1840)		161 (50)		<0.0001
SHEPHERD (52 weeks)	−1909 (−1795)		N/A		<0.0001
Units of PRBC transfused: mean (median)					
	Before	During	Before	During	

	Eculizumab		Placebo		p-value
	treatment	treatment	treatment	treatment	
TRIUMPH (26 weeks)	9.6 (9.0)	3.0 (0.0)	9.7 (8.5)	11.0 (10.0)	<0.0001
SHEPHERD (52 weeks)	15.9 (8.0)	5.9 (0.0)	N/A	N/A	<0.001
E05-001 (median 22 months)	8.7 (8.0)	2.8 (0)	N/A	N/A	
Hb stabilisation: n/N (%)					
TRIUMPH (26 weeks)	21/43 (48.8%)		0/44 (0%)		<0.0001
Transfusion avoidance: n/N (%)					
TRIUMPH (26 weeks)	22/43 (51.2%)		0/44 (0%)		<0.0001
SHEPHERD (52 weeks)	49/97 (51.0%)		N/A		<0.001
TE: n/N (%)					
	Baseline	During treatment	Baseline	During treatment	
TRIUMPH (26 weeks)	9/43 (20.9%)	0/43 (0%)	8/44 (18.2%)	1/44 (2.3%)	
SHEPHERD (52 weeks)	42/97 (43.3%)	2/97 (2.1%)	N/A		
E05-001	63/195 (32.3%)	NR/195	N/A		
Deaths: n/N (%)					
TRIUMPH (26 weeks)	0/43 (0%)		0/44 (0%)		
SHEPHERD (52 weeks)	1/97 (1.0%)		N/A		
E05-001	2/195 (1.0%)		N/A		

Eculizumab was associated with some improvements in quality of life (QoL), notably fatigue.

The submission claimed superiority of eculizumab over best supportive care (BSC) in decreasing life threatening thromboembolic (TE) events and deaths.

There were no deaths reported in either the eculizumab or placebo groups in the 26-week TRIUMPH trial. The claim of superiority of eculizumab over BSC in reducing deaths was based on comparison of

a) the sum of the number of deaths observed among eculizumab patients in the 26-week controlled TRIUMPH trial (no deaths), the 52-week uncontrolled SHEPHERD study (one death), the 12-week uncontrolled PILOT study (no deaths) and the 2-year E05-001 (2 deaths); and
b) the 2-year mortality rate of patients receiving BSC estimated from a 25-year follow-up study (Hillmen 1995) of 80 PNH patients referred to a UK hospital between 1940 and 1970.

The information on mortality in patients receiving eculizumab treatment was limited to patients with 2 years of exposure to eculizumab.

Serious infection, primarily meningococcal infection, was the main safety concern of eculizumab and is related to the mechanism of action. Headache was the most common adverse event and appeared to decrease over time.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that eculizumab is therapeutically superior to best supportive care with similar safety issues.

The PBAC did not accept this claim based on the evidence presented.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

Based on the comparison of the 2-year mortality rate of paroxysmal nocturnal haemoglobinuria (PNH) patients receiving eculizumab and the 2-year mortality rate of PNH patients receiving standard care (estimated from Hillmen, 1995), the submission presented an estimate of drug cost per additional death avoided.

The incremental cost effectiveness ratio (ICER) was estimated to be greater than $200,000 per additional death avoided over a 2 year period.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated to be between $30 – 60 million in Year 5 of listing.

12. Recommendation and Reasons

The PBAC acknowledged that much of the evidence provided in the submission comes from well designed and well controlled studies conducted in the context of a very rare disease. Notwithstanding, the Committee had a number of concerns about the adequacy of the evidence for assessing the comparative effectiveness, safety and cost-effectiveness of eculizumab as required by the *National Health Act.*

Firstly, the direct evidence from the placebo controlled clinical trials is limited to data on transfusions avoided and haemoglobin stabilisation. The claim of superiority in decreasing life threatening thromboembolic events (TE) cannot be adequately supported by the results of the placebo controlled studies and relies upon a comparison of TE events before- and after-eculizumab treatment. Although the Committee agreed that the use of a before- and after-comparison was not unreasonable in this very rare condition, they were concerned that this approach introduced a bias in favour of eculizumab. This is because, of the total population with paroxysmal nocturnal haemoglobinuria (PNH), those patients who had recently experienced a TE event are more likely to have been entered into the clinical trial than those who had not, thus elevating the before- TE event rate above the norm in this highly variable condition. The Committee considered that one means of reducing this bias would be to provide more than one year of pre-treatment TE data for the clinical trial cohort.

Secondly, even if the reduction in TE events attributable to eculizumab treatment was able to be better quantified than currently, it is not clear how this will translate into a mortality benefit. The survival data for paroxysmal nocturnal haemoglobinuria patients receiving eculizumab are based on an uncontrolled follow-up study (E05-01) and the mortality rate for patients receiving eculizumab beyond 2 years is not clear. The survival data for paroxysmal nocturnal haemoglobinuria patients receiving best supportive care may not be fully represented by the Hillman (1995) study population of 80 patients referred to a UK hospital between 1940 and 1970 and receiving standard care of the period.

The PBAC noted that survival in paroxysmal nocturnal haemoglobinuria patients, even without eculizumab, can be reasonably long and quite variable. In 5 cohort studies, age at diagnosis ranged from 30 – 45 years; median survival after diagnosis in the most recent study (Nishimura, 2004) was 23 – 25 years with approximately 44% of patients surviving for more than 25 years (using current supportive care options). Spontaneous clinical remission also occurred in some patients.
Noting that the sponsor acknowledges that improved best supportive care has improved patient survival over this period, the PBAC agreed with the ESC that the mortality estimate from Hillmen represents the most pessimistic estimate of survival from the available cohort studies.

Thirdly, the Committee was not satisfied that the comparative toxicity of eculizumab was adequately elucidated. Despite measured improvements in Quality of Life (particularly fatigue), more patients in the eculizumab arm of the TRIUMPH study reported fatigue as an adverse event. Two cases of meningococcal infection occurred in clinical trials despite immunisation and longer term safety data is very limited.

The PBAC therefore considered the submission's estimated cost per additional death avoided over a 2-year period of greater than $200,000 to be unacceptably high and highly uncertain, and rejected the submissions request for listing on the PBS on this basis.

The PBAC further considered that, based on the presently available data, eculizumab does not meet criteria (2), (4), (5) or (10) for listing on the Life Saving Drugs Program. Specifically, not all patients with paroxysmal nocturnal haemoglobinuria appear to have a significantly reduced lifespan (with approximately 44% of patients surviving for more than 25 years), and the evidence that eculizumab treatment extends lifespan is equivocal; it is not clear if some of the co-morbidities experienced by patients with paroxysmal nocturnal haemoglobinuria (eg aplastic anaemia, myelodysplastic syndromes, leukaemia, renal failure etc) might compromise the effectiveness of eculizumab; the clinical effectiveness of eculizumab in reducing mortality is not accepted and eligibility criteria are not yet available for review.

The Committee however considered that there may be a subgroup of patients with paroxysmal nocturnal haemoglobinuria in whom the benefit of treatment with eculizumab is substantial, but that it is not possible to identify this group at the present time. The Committee noted that in this context, the pre-PBAC response indicates the sponsor is working on a set of eligibility criteria to identify the population of patients that will benefit most from treatment with eculizumab.

The Committee therefore agreed that eculizumab may meet the criteria for the Life Savings Drugs Program (LSDP) for a subgroup of patients with paroxysmal nocturnal haemoglobinuria, but given that it is not possible to identify this subgroup at the present time, the PBAC rejected the current application for consideration for the LSDP.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the

medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor disagrees with the PBAC's current position, especially in regard to the survival threat for patients suffering untreated PNH and the potential of eculizumab therapy for those patients most at risk . The sponsor is committed to working with the PBAC to address any areas of their uncertainty which require clarification.