PUBLIC SUMMARY DOCUMENT
Product: Eculizumab, solution concentrate for I.V. infusion, 300 mg in 30 mL, Soliris®
Sponsor: Alexion Pharmaceuticals Australasia Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) PBS listing, or a recommendation for inclusion on the Life Saving Drugs Program (LSDP) 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.

Life Saving Drugs Program
The Commonwealth Government provides funds under an appropriation item established for the specific purpose of assisting access to expensive and lifesaving drugs accepted by the PBAC as clinically effective, but not available as pharmaceutical benefits because of a failure to meet cost effectiveness criteria. Financial assistance for such drugs is approved in accordance with specified eligibility criteria and subject to certain conditions as agreed by the Ministers for Health and Finance.

2. Background

At the July 2008 meeting, the PBAC rejected the application for Section 100 listing of eculizumab for the treatment of patients with PNH on the basis of an unacceptably high and highly uncertain estimated cost per additional death avoided over a 2-year period.

The PBAC also rejected this application for consideration for the LSDP. The Committee agreed that eculizumab may meet the criteria for the LSDP for an as yet unidentified subgroup of patients with PNH, but that it was not possible to identify this subgroup at the present time. The Committee noted the sponsor's indication that it was working on a set of eligibility criteria to identify a population of patients that would benefit most from treatment with eculizumab.

The Public Summary Document for eculizumab from the July 2008 meeting can be accessed from
http://www.health.gov.au/internet/main/publishing.nsf/Content/211923B8041DA9D2CA2574EF00060D0C/$File/Eculizumab%20Final%20PSD%20Alexion%20Pharmaceuticals%20Inc.pdf

3. Registration Status

Eculizumab was TGA registered on 20 March 2009 for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) 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 for treatment of paroxysmal nocturnal haemoglobinuria to reduce haemolysis.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Paroxysmal nocturnal haemoglobinuria is a clonal haemopoietic stem cell disorder that is extremely rare, progressive and life-threatening. Complement mediated intravascular haemolysis is the central mechanism responsible for morbidities and mortality in PNH including thromboembolism, renal dysfunction, pulmonary hypertension, severe anaemia and disabling fatigue.

Currently, therapeutic management of PNH is supportive and mainly addresses the treatment of anaemia and prevention of thrombotic events.

Eculizumab would provide a treatment option for patients with PNH to reduce haemolysis, however it is not curative for the underlying disease.

6. Comparator

The submission nominated supportive care as the main comparator. The comparator was accepted, as previously, by the PBAC as appropriate.

7. Clinical Trials

The submission presented the same clinical trial evidence as in the submission to the July 2008 PBAC meeting. One 26 week randomised placebo controlled trial (TRIUMPH), two uncontrolled single arm eculizumab studies (52 week SHEPHERD and 12 week PILOT) and the E05-001 extension study (median duration 22 months) were presented.

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

Trial/First author	Protocol title/ Publication title	Publication citation
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

At the July 2008 meeting the PBAC considered that the direct evidence from the TRIUMPH trial to establish the superiority of eculizumab in clinical effectiveness was limited to transfusions avoided and Hb stabilisation, and claimed benefits in terms of fewer thromboembolic events, fewer deaths and improved kidney function were not adequately demonstrated.

The re-submission presented new data regarding the effect of eculizumab on kidney function and damage of other end-organs. The key additional *post hoc* analyses of severe morbidity events of individual end-organs before and during eculizumab treatment in extension study E05-001 are summarised below:

End-organ	Pre-treatment (1683 pt-years)		During treatment (382 pt-years)		P-value	Relative rate reduction	*Absolute difference (events/100 pt-yrs*
	No. of events	Events/ 100 pt-yrs	No. of events	Events/ 100 pt-yrs			
Brain	29	1.72	4	1.05	NS	39%	*0.67*
Liver	52	3.09	8	2.10	NS	32%	*0.99*
GI	66	3.92	3	0.79	Sig	80%	*3.13*
Kidney	71	4.22	8	2.10	Sig	50%	*2.12*
TE	124	7.37	5	1.31	Sig	82%	*6.06*
Compo-site*	271	16.10	28	7.34	Sig	54%	*8.76*

* Composite Severe Morbidity Event included non-overlapping events in the 5 most common systems - brain, liver, GI, renal and thrombosis

The proportions of patients with events were not reported, except for pre-treatment thromboembolic events, 31.8% (62/195). The claim of long-term improvement in end-organ function and therefore survival with eculizumab treatment is based on post-hoc before and after comparisons in the uncontrolled E05-001 study with median treatment duration of 22 months.

At the July 2008 meeting, the PBAC was not satisfied that the comparative toxicity of eculizumab and BSC was adequately elucidated, as two non-fatal cases of meningococcal infection occurred despite immunisation in the clinical trial/studies and longer term safety data were very limited.

No new toxicity data were presented in the re-submission except for one additional death reported in study E05-001 and the inclusion of PSUR 2 (10 reported deaths and 1 fatal meningococcal infection case during the 6-month reporting period).

9. Clinical Claim

The re-submission claimed that eculizumab is therapeutically superior to best supportive care for the treatment of PNH to reduce morbidity and mortality with similar safety issues.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The economic evaluation was updated, using the proposed new effective price and 3-year mortality rates for patients receiving eculizumab (from the included eculizumab trial/studies) and BSC (derived from de Latour 2008 study). In the previous submission the incremental cost effectiveness ratio (ICER) was estimated to be greater than $200,000 per additional death avoided over a two year period, whilst in the re-submission the incremental cost effectiveness ratio (ICER) was also estimated to be greater than $200,000 per additional death avoided over a three year period

In the previous submission, neither costs nor outcomes were discounted. In the current re-submission, only costs but not outcomes were discounted.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated to be $10-$30 million in Year 5
The likely number of patients per year was estimated to be less than 10,000 in Year 5.

The PBAC considered the utilisation of eculizumab for PNH was also uncertain as the extent of under diagnosis of PNH in Australia is unclear and there was uncertainty in the applicability of the UK incidence and prevalence to the Australian population

12. Recommendation and Reasons

The comparator of best supportive care (BSC) was accepted, as previously, by the PBAC as appropriate. The submission presented the same clinical trial evidence as in the submission to the July 2008 PBAC meeting. One 26 week randomised placebo controlled trial (TRIUMPH), two uncontrolled single arm eculizumab studies (52 week SHEPHERD and 12 week PILOT) and the E05-001 extension study (median duration 22 months) were presented. The Committee considered that uncertainty remained in the difference in mortality of patients receiving eculizumab and those receiving best supportive care and in the magnitude of the absolute benefit of eculizumab over best supportive care in reduction of thromboembolic events. The effectiveness of eculizumab in preserving end-organ function was also not clear as improvements were based on post-hoc before and after comparisons in the uncontrolled E05-001 extension study and there was still concern about the lack of long-term clinical effectiveness data.

The PBAC considered that the evidence presented was not sufficient to support the claim of similar safety of eculizumab to best supportive care due to the lack of long term placebo controlled trials. The increased risk of meningococcal infection with eculizumab treatment remained a concern, especially the increased risk of contracting meningococcal strain B infection for which there is no vaccine available. Although the submission claimed that eculizumab reduced PNH related fatigue, the potential for patients to experience fatigue as an adverse effect of treatment with eculizumab was noted, as fatigue was acknowledged in the submission as a moderate to severe symptom of PNH which causes significant patient distress.

The Committee considered that, with an annual drug cost approaching $500,000 per year, the incremental cost per additional death avoided was unacceptably high and uncertain. The utilisation of eculizumab for PNH was also uncertain as the extent of under diagnosis of PNH

in Australia is unclear and there was uncertainty in the applicability of the UK incidence and prevalence to the Australian population.

The PBAC noted the advice from the Highly Specialised Drugs Working Party that again supported listing of eculizumab under the Highly Specialised Drugs Program subject to meeting clinical and cost effectiveness criteria.

However, the PBAC rejected listing eculizumab on the PBS on the basis of an unacceptably high and highly uncertain cost-effectiveness.

In relation to the criteria for inclusion on the Life Saving Drugs Program (LSDP), the Committee accepted that PNH may shorten the lifespan of some patients suffering from the disease and that the submission's proposed link between treatment with eculizumab resulting in the reduction of thromboembolic events and an improved lifespan of some patients with PNH was not unreasonable (Criterion 2). The PBAC accepted eculizumab is safe to use in patients with bone marrow dysfunction and chronic kidney disease and hence that Criterion 4 for the LSDP was met. The Committee considered that eculizumab may be clinically effective for some patients with PNH, and hence that the drug meets Criterion 5 of the LSDP. With regard to Criterion 10 of the LSDP, the PBAC considered that the proposed funding algorithm did not clearly identify those patients with PNH who would most benefit from treatment with eculizumab, however that criteria for initiation and continuation of treatment with eculizumab could be developed to identify those patients with PNH who would benefit most from treatment with eculizumab.

The PBAC therefore considered that eculizumab meets the criteria for inclusion on the LSDP but that specific requirements for initiation and continuation of treatment would need to be developed by independent experts to identify those patients with paroxysmal nocturnal haemoglobinaemia (PNH) who would benefit most from treatment with eculizumab.

The PBAC noted that although eculizumab meets the criteria for the LSDP, the inclusion of eculizumab on LSDP would mean a new direction for that program, as the disease being treated is not a rare inherited enzyme deficiency, for which the LSDP was established. The PBAC also noted the steep escalation of costs associated with recent applications for consideration of drugs under the LSDP.

The PBAC noted that the submission meets the criteria for an Independent Review.

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 agrees that eculizumab is an appropriate drug to be listed and funded under the Life Savings Drug Program. It is Alexion's intent to work closely with the LSDP and the Health Ministry to find rapid solutions for access to funded eculizumab therapy for patients at highest risk from this ultra-rare, destructive, progressive and life threatening disease of PNH.

We look forward to creating a unique and sustainable funding model for the LSDP and eculizumab in PNH, for all stakeholders; from Government to patients.