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: July 2010

1. Purpose of Application

To request the PBAC:

- provide advice to the Minister regarding the suitability of eculizumab for inclusion on the Life Saving Drugs Program (LSDP) for treatment of paroxysmal nocturnal haemoglobinuria (PNH) under the revised LSDP funding criteria and conditions;
- consider the proposed initiation and continuation criteria for eculizumab for the LSDP which endeavours to identify those patients with PNH who would benefit most from treatment with eculizumab.

Through the LSDP, the Australian Government provides subsidised access, for eligible patients, to expensive and potentially life saving drugs for very rare life-threatening conditions. Before a drug is made available on the LSDP, it must generally be accepted by the Pharmaceutical Benefits Advisory Committee as clinically necessary and effective, but not recommended for inclusion on the Pharmaceutical Benefits Scheme due to unacceptable cost-effectiveness. On 10 May 2010, the criteria for inclusion on the LSDP were revised.

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 the July 2008 application for consideration for the LSDP. The Committee agreed that eculizumab might meet the criteria for the LSDP for an as yet unidentified subgroup of patients with PNH, but that it is 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.

At the March 2009 meeting, the PBAC again rejected listing eculizumab on the PBS, on the basis of unacceptably high and highly uncertain cost-effectiveness.

However, the PBAC considered that eculizumab met the criteria for inclusion on the LSDP.

For full details, see the July 2008 and March 2009 Public Summary Documents.

3. Registration Status

Eculizumab was registered by the TGA on 17th February 2009 for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) to reduce haemolysis.

4. Listing Requested and PBAC's View

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, with limited evidence of efficacy of these basic standard care methods.

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

6. Comparator

At the July 2008 meeting, the PBAC agreed that supportive care is the appropriate comparator.

7. Clinical Trials

The submission addressed each of the revised LSDP funding criteria and conditions, and re-presented data from the March 2009 submission to support the claim that eculizumab satisfied each of the revised criteria and conditions for PNH.

The submission also presented an updated literature search, which identified two new studies not included in the March 2009 submission (Weitz et al. and Helley et al.).

Details of the published studies identified in the submission are presented in the following table.

Trial ID/First author	Protocol title/ Publication title	Publication citation
Hillmen P, et al	Natural history of paroxysmal nocturnal haemoglobinuria.	N Engl J Med 1995; 333(19): 1253-8
de Latour RP, et al	Paroxysmal nocturnal haemoglobinuria: natural history of disease subcategories.	Blood 2008; 112(8): 3099-106
Nishimura J, et al	Clinical course and flow cytometric analysis of paroxysmal nocturnal haemoglobinuria in the United States and Japan.	Medicine (Baltimore) 2004; 83(3): 193-207
Socie G, et al	Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors.	Lancet 1996; 348(9027): 573-7
Parker C, et al	Diagnosis and management of paroxysmal nocturnal haemoglobinuria.	Blood 2005; 106(12): 3699-709
Hillmen P, et al	Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal haemoglobinuria.	Blood 2007; 110(12): 4123-8
Fowkes FJ, et al	Incidence of diagnosed deep vein thrombosis in the general population: systematic review.	Eur J Vasc Endovasc Surg 2003; 25(1): 1-5
Kanakura Y, et al	Safety and efficacy of the terminal complement inhibitor eculizumab in Japanese patients with paroxysmal nocturnal haemoglobinuria: AEGIS Phase II Clinical Study Results.	ASH Annual Meeting Abstracts 2008; 112(11): 3438

Trial ID/First author	Protocol title/ Publication title	Publication citation
Hill A, et al	Nitric oxide consumption and pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria.	American Society of Haemotology 2005 (Abstract)
Machado RF, et al	N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease.	JAMA 2006; 296(3): 310-8
Hillmen P, et al	Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal haemoglobinuria.	American Journal of Hematology 2010; 85(8): 553-9
Hill A, et al	Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria.	British Journal of Hematology 2010; 149(3): 414-425
Rother RP, et al	Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal haemoglobinuria.	Nat Biotechnol 2007; 25(11): 1256-64
Weitz IC, et al	Thrombosis in Paroxysmal Nocturnal Haemoglobinuria – insights into the role of complement in thrombosis.	Thrombosis Res. 2010 Apr; 125 Suppl 2:S106-7.
Helley D, et al	Evaluation of hemostasis and endothelial function in patients with paroxysmal nocturnal haemoglobinuria receiving eculizumab.	Haematologica 2010 Apr; 95(4):574-81
Hillmen P, et al	The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobionuria.	N Engl J Med 2006; 355(12): 1233-43
Hillmen P, et al	Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal haemoglobinuria.	N Engl J Med 2004; 350(6): 552-9
Brodsky RA, et al	Multicentre phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal haemoglobinuria.	Blood 2008; 111(4): 1840-7

8. Results of Trials

A summary of the arguments from the submission in support of eculizumab for PNH meeting the revised LSDP criteria is presented below:

Criterion 3 stated:

Epidemiological and other studies provide evidence acceptable to the PBAC that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease.

The submission argued that the PSD for the March 2009 submission stated, "*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 therefore considered that PNH has met Criterion 3. The submission noted that the median age of onset of PNH was 30-40 years, and that following diagnosis the five-year mortality rate for patients with PNH ranged from 15% to 35% and the ten-year mortality ranged from 24% to 48%.

Criterion 4 stated:

There is evidence acceptable to the PBAC to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug.

The submission claimed that the following recommendation from the March 2009 PSD supported the argument that PNH as a disease meets this reworded criterion in the newly implemented criterion: *"…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 submission's argument that treatment with eculizumab was associated with an extension of life in PNH patients, was based on the claim it reduced life-threatening complications of PNH including thrombosis, kidney damage, pulmonary hypertension, ischemic brain damage, liver and gastrointestinal organ damage. This argument was consistent with those made in the previous submissions to the PBAC.

The submission used the Weitz et al. and Helley et al. studies as additional evidence to support eculizumab's qualification for criterion 4 of the revised funding criteria. The submission stated that these studies demonstrate that complement mediated haemolysis leads to chronic activation of both the inflammatory and coagulation pathways, ultimately explaining why PNH patients have an increased number of thromboembolic events, severe morbidities and early mortality. The submission reported that both studies demonstrated evidence that treatment with eculizumab reduced haemolysis ($P<0.001$) and measures of inflammation (interleukin (IL)-6: $P=0.04$) and haemostatic activation (D-dimer: $P\leq0.01$) in these patients.

The submission presented the same funding algorithm with initiation and continuation requirements as in the March 2009 submission. These were developed by experienced PNH experts and clinicians in response to PBAC's March 2008 recommendation that criteria were needed to identify those PNH patients who would most benefit from eculizumab therapy.

The submission stated its support for the prompt appointment of a panel of independent experts to reconfirm the already developed expert criteria, which identify those patients with PNH who would benefit most from treatment with eculizumab.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that eculizumab was an effective therapy that directly targeted the life threatening consequences of PNH and transformed the quality of patients' lives, with evidence that eculizumab substantially extended the lifespan of treated patients.

For PBAC's view, see Recommendation and Reasons.

10. Estimated PBS Usage and Financial Implications

The submission provided updated usage and financial costs and estimated less than 10,000 patients in Year 5 of listing at a cost to Government of $30 – $60 million in Year 5. The commentary considered the submission's financial estimates are highly uncertain and are likely to be under-estimated because only drug acquisition costs have been included in the estimates.

The only change in estimated financial implications between the current submission and the March 2009 submission is the use of revised uptake rates, which results in higher estimates of the eligible patient population.

11. Recommendation and Reasons

The PBAC deferred the submission for eculizumab to allow the sponsor time to obtain further data about the magnitude of the survival gain before making a decision on whether eculizumab substantially extends a patient's lifespan as per criterion 4 of the Life Saving Drugs Program (LSDP).

The PBAC considered that the historical control data presented in the submission (Hillmen 1995, Socie 1996, Nashimura 2004 and de Latour 2008) may not reflect recent best supportive care practice and that best supportive care has improved over the years. The PBAC noted there have been many improvements in the treatment of thromboembolic events as well as the treatment of iron overload and anaemia.

The PBAC noted that patient mortality of the historical controls at 10 years had decreased, as reported by Hillmen (1995) as 48% and 24% by de Latour (2008). The de Latour study included a mix of patients with classic PNH, intermediate and aplastic anaemia-PNH (AA-PNH) who were diagnosed between 1950 and 2005. The PBAC noted that 35% of patients were diagnosed prior to 1986, 31% between 1986 and 1995 and 33% after 1995. The Kaplan-Meier curve plotted survival for the global population, for the three sub-categories of PNH and for the three different time periods over which the data were collected. However, only survival for AA-PNH was plotted for the three different time periods, and these data demonstrated improved survival rates for patients diagnosed with AA-PNH after 1995. As a result, the PBAC was uncertain that the magnitude of the survival benefit for eculizumab was substantial when compared with modern best supportive care. However, the AA-PNH population may not be reflective of the group of patients for whom treatment with eculizumab is intended under the LSDP, i.e. classic PNH. Therefore, the PBAC considered that further information about recent historical controls (from 1995 onwards) with similar characteristics to those now treated with eculizumab, and relevant to the group of patients proposed for access in Australia, would provide better matched control data for the eculizumab treated group. As more recently diagnosed patients are also likely to be younger, it would be most informative to have the historical control data from a source such as the de Latour study published in 2008 presented along the following lines:

(a) confirmation that no patient in the cohort received eculizumab during the period of follow-up being reported;
(b) for the subgroup of classical PNH patients only, but further sub-categorised into three groups according to year of diagnosis:
    - recent (eg since 1996)
    - intermediate (eg 1986 to 1995) and
    - more distant (eg 1985 or before);
(c) for each sub-category, a description of the characteristics of the included patients including the number of patients, proportion of males, age at diagnosis (mean and distribution), year of diagnosis (mean and distribution) and preferably also other characteristics which were included in the proposed eligibility and initiation criteria for the Phase III randomised trial and/or the LSDP because of their prognostic value;

(d) on a single figure, as exemplified by Figure 1(c) on page 3101 of the de Latour (2008) paper, the three Kaplan-Meier plots of overall survival representing each sub-category;
(e) and, preferably, the 3-year and/or 10-year survival rates for each sub-category (as a complement to, but not a substitute for, the requested Kaplan-Meier plots).

The PBAC was satisfied that eculizumab meets all the other new LSDP criteria. With respect to Criterion 4, the PBAC accepted that patients with classic PNH were demonstrated in epidemiological and other studies to have a significant reduction in age-specific life expectancy. The PBAC also noted the data presented to address Criterion B1, showed that the price proposed for eculizumab in Australia is less than prices paid overseas. The PBAC also noted the comparison with other drugs funded under the LSDP (Criterion B2) showing the price is less for adults than other drugs in the Program.

Recommendation
Defer

Further Information
Further to the PBAC's consideration of this product at the July 2010 meeting (at which the Committee deferred the submission to allow the sponsor time to obtain further data about the magnitude of the survival gain), the sponsor presented a re-submission to the PBAC Special Meeting held in August 2010.

The re-submission addressed questions from the PBAC pertaining to the de Latour manuscript, with a focus on PNH mortality rates described in de Latour (2008).

The PBAC noted the additional data of three-year mortality rates for all paroxysmal nocturnal haemoglobinuria patients from de Latour (2008) provided by the sponsor in support of the request to list eculizumab on the Life Saving Drugs Progam for the treatment of PNH. As requested by the PBAC, the data was categorised into three groups according to year of PNH diagnosis – diagnosis in 1985 or before, between 1986 and 1995 and between 1996 and 2005. The PBAC noted that the survival rates for this three-year period of follow-up appeared consistent across the three groups based on year of diagnosis, however that no further disaggregation of these data had been provided for the type of PNH (classic, intermediate and aplastic anaemia PNH). The sponsor had also confirmed that the data from the de Latour study were not confounded to any material extent by use of eculizumab during the follow-up period.

The PBAC considered that the additional evidence, including that presented by the sponsor and unpublished data, acceptably supported the prediction that a patient's lifespan with classic PNH would be substantially extended as a direct consequence of treatment with eculizumab compared to best supportive care and hence concluded that criterion four of the LSDP was now met.

The PBAC considered that the history component of the proposed treatment funding algorithm should be limited to include only patients with a history of either thrombosis or transfusion of four or more units in the most recent 12 months. However, further advice should be sought from the clinical advisory committee on the remaining five proposed alternative history criteria to be justified on the basis of unambiguously identifying patients

likely to benefit most from treatment with eculizumab. For example, the PBAC considered that inclusion of fatigue as an alternative in these criteria may not be appropriate, as it is likely that the majority of patients with any form of PNH could qualify under this criterion, rather than those patients with PNH who would be most likely to gain an extension in their lifespan from treatment with eculizumab. A comparison of corresponding funding algorithms and their rationales from other similar jurisdictions overseas may also be informative in this regard.

The PBAC considered that patients funded under the LSDP, including those to be grandfathered, should be required to meet the more limited qualification criteria for treatment as modified by the PBAC from those specified by the clinical advisory committee. The PBAC considered that PNH patients currently receiving treatment through compassionate access schemes should continue to receive treatment through compassionate access should they not meet the LSDP qualification criteria

12. 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.

13. Sponsor's Comment

Alexion welcomes the PBAC's recommendation that Soliris now meets the revised criteria, (effective May 10th 2010), for consideration of funding via the LSDP by Government. We look forward to working with the Department of Health and Ageing and Government to ensure an expedited review of possible funding arrangements and to ensure urgent funded access to Soliris therapy for PNH patients who will most benefit will be achieved expeditiously.