Australian Government
Department of Health and Aged Care

Life Saving Drugs Program (LSDP): Review of Medicines for Paroxysmal Nocturnal Haemoglobinuria (PNH)

Review summary and Expert Panel recommendations

Purpose of the PNH Review

Eculizumab (Soliris®) was listed on the LSDP for PNH on 1 January 2011. The Expert Panel considered this review at its October 2020 meeting.

This review of eculizumab sought to develop a better understanding of this LSDP medicine by comparing its current use against the recommendations and expectations at the time of listing.

The review further aimed to assess the clinical benefits achieved through the use of eculizumab; ensure the ongoing viability of the LSDP; and ensure testing and access requirements for eculizumab remain appropriate. It identified immediate and future changes that may be required to the funding criteria for eculizumab and to the LSDP more broadly.

The review of each of the LSDP medicines was supported by an approved disease specific Review Protocol, which was structured around seven Terms of Reference (ToRs). The ToRs were tailored specifically to each disease and the relevant medicine(s).

PNH Medicine Review Terms of Reference

1. Review the prevalence of PNH in Australia.
2. Review evidence for the management of PNH and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of eculizumab on the program (including the validity of the tests).
3. Review clinical effectiveness and safety of eculizumab for the treatment of PNH, including analysis of LSDP patient data and international literature to provide evidence of life extension.
4. Review relevant patient based outcomes that are most important or clinically relevant to patients with PNH.
5. Assess the value for money of eculizumab under the current funding arrangements by evaluating the benefit of its treatment outcomes and cost.
6. Review the utilisation of eculizumab including storage, dispensing and evidence of patient compliance to treatment.
7. Investigate developing technologies that may impact future funded access.

Key Findings and Recommendations from the Expert Panel

ToR 1 – Review the prevalence of PNH within Australia

The Expert Panel noted the Report's estimate of prevalence for PNH disease to be 0.5 per 50,000 people and the sponsor's estimate to be 0.8 per 50,000. The Expert Panel noted the number of patients requiring ongoing treatment for PNH is likely to continue to rise at a rate higher than population growth. Estimates of the prevalence of PNH should therefore be revisited periodically.

Due to the eligibility criteria limiting use of treatment to patients with the classic disease presentation, approximately 63 to 77 percent of patients with PNH in Australia were estimated to be eligible for access to LSDP subsidised treatment. 53 to 84 percent of these eligible patients with PNH were accessing treatment on the LSDP.

Recommendation 1:

The Expert Panel considered that PNH meets the prevalence criterion of less than 1:50,000 and on that criterion currently remains suitable for inclusion on the LSDP.

In light of the increasing number of PNH patients in Australia, the Expert Panel recommended that the prevalence of PNH be reviewed again within five years to determine whether PNH continues to meet the definition of a rare disease for the purposes of this program.

ToR 2 – Review evidence for the management of PNH and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of eculizumab on the program (including the validity of the tests)

The Expert Panel noted the current LSDP patient eligibility criteria (for both initiating and continuing patients) were the requirements for subsidised treatment but were not intended to be general guidelines for management of PNH. This explained some differences between LSDP eligibility criteria and international guidelines.

The most prominent difference between availability of eculizumab on the LSDP and international recommendations for the use of eculizumab in patients with PNH related to the dose and the dosing interval. Consistent with the Therapeutic Goods Administration (TGA)-approved Product Information for eculizumab, the maximum dose subsidised through the LSDP was 900 mg every second week. This differed from international guidelines that recommend adjustment of the dose and the interval between doses as required to minimise the risk of haemolysis. Higher and/or more frequent doses than described in the Product Information may be required in a minority of patients to minimise risk of haemolysis.

The limits imposed on dosing of eculizumab by the LSDP were a concern for some patients. Dose adjustments are often clinically appropriate to maximise health outcomes, but these adjustments generated higher LSDP program costs. For patients requiring higher doses and/or more frequent dosing of eculizumab, the costs to generate the expected health gains were higher than was estimated at the time eculizumab was listed on the LSDP.

Recommendation 2:

The Expert Panel advised that to improve care for patients, the LSDP Guidelines for PNH be adjusted to specify that the frequency of dosing of eculizumab can be +/- 2 days from the 14 day interval, as outlined in the Product Information.

Recommendation 3:

The Expert Panel advised that the Product Information should be updated to include guidance on the use of eculizumab doses greater than 900mg per infusion in patients with PNH (notably, in the event of breakthrough intravascular haemolysis). If the Product Information is updated, then it would be appropriate for this guidance to be incorporated in the LSDP Guidelines for PNH. This will require reconsideration of costs and renegotiation of price.

ToR 3 – Review clinical effectiveness and safety of eculizumab for the treatment of PNH, including analysis of LSDP patient data and international literature to provide evidence of life extension

The Report indicated eculizumab improves disease control and some measures of quality of life (QoL) in patients.

The Review's modelled estimates of survival gain in patients with PNH treated with eculizumab on the LSDP were consistent with modelled estimates reported in the published literature. The evidence also appeared to be consistent with that presented to the Pharmaceutical Benefits Advisory Committee (PBAC) prior to inclusion of eculizumab on the LSDP. Comparisons of survival outcomes between patients on the LSDP and other natural history modelled data demonstrated there was considerable uncertainty around the extent of survival benefit attributable to eculizumab, with likely overestimation of the benefit. Although eculizumab would have been a significant contributor to observed improvements in survival, full attribution of the observed improvement to the use of eculizumab may not be reasonable given other improvements in standard of care have been implemented over time.

ToR 4 – Review relevant patient based outcomes that are most important or clinically relevant to patients with PNH

Consultations with stakeholders, including consumers, indicated the outcomes that are most important to patients include improvement in symptoms which affect QoL.

The Expert Panel noted data collection on the LSDP was incomplete and seen as burdensome and non-essential by some key stakeholders. Other stakeholders considered data collection was important for quality care. The LSDP patient application process may be difficult for prescribers unless they have multiple patients and are familiar with the program.

Noting the current issues with completeness of data provision, the cost of the medicine, and the costs associated with program compliance and administration, the Expert Panel considered simplification of the patient application and reapplication process may improve the experience for patients and prescribers and improve completeness of essential data collection.

Recommendation 4:

The Expert Panel noted that, as for other diseases included in the LSDP, the extent and methods of data collection and the approach to analysis of the data required improvement. In comparison with other diseases included in the LSDP, the level and

complexity of detail in data collection was lower and was comparable with that used for authority listings on the Pharmaceutical Benefits Scheme (PBS). The Expert Panel recommended that data collection be streamlined wherever possible.

ToR 5 – Conduct an analysis of the value for money of eculizumab under the current funding arrangements by evaluating the benefit of its treatment outcomes and cost

The average cost per patient per year for eculizumab was approximately $[redacted] per annum. The calculated cost/Life Year Gained (LYG) from modelling in the Report was estimated at approximately $[redacted]. This calculation had significant uncertainty and was likely an underestimate but indicated an extremely high cost paid for the health gains achieved. LSDP expenditure on eculizumab for patients with PNH was approximately $[redacted] in 2018. The Expert Panel noted expenditure on eculizumab for PNH constituted a substantial proportion of the LSDP budget. In fact, eculizumab had the largest share of the LSDP budget by a large margin.

Both cost per patient per year and calculated cost/LYG compared unfavourably to several other LSDP funded therapies.

The Expert Panel also noted in December 2014, eculizumab was PBS-listed for patients with a different condition, atypical haemolytic uremic syndrome (aHUS). Eculizumab was different from all other medicines included on the LSDP in this regard (i.e. in having both PBS and LSDP listings for different conditions). This also meant the market for this medicine was not limited to a single rare condition. Government expenditure for eculizumab on the PBS for patients with aHUS was approximately $[redacted] in 2019-20.

Recommendation 5:

The Expert Panel noted that although there appeared to be a survival gain and improvement in QoL associated with eculizumab treatment, the cost of eculizumab was extremely high in absolute terms and relative to other medicines on the LSDP. The Expert Panel could identify no specific justification for this extremely high cost and considered that the cost per patient should reduce to levels more aligned with costs paid for similar health gains generated by treatments for other rare diseases on the LSDP and in other subsidy schemes. This would improve equity and sustainability in the system. The Expert Panel therefore recommended that the listing arrangements be reassessed with the goal of improving value for money when:

(i) current deeds of agreement with the sponsor expire; and/or

(ii) new medicines for PNH are considered for entry onto the LSDP or other subsidy programs; and/or

(iii) changes in maximum maintenance dose of eculizumab are implemented for patients experiencing breakthrough haemolysis.

Recommendation 6:

The Expert Panel recommended that there be reconsideration of the appropriateness of inclusion on the LSDP of any medicine that has a listing on the PBS for another condition resulting in a total patient market in Australia that exceeds the threshold for medicines to be eligible for inclusion on the LSDP (i.e. prevalence < 1:50,000).

ToR 6 – Review the utilisation of eculizumab, including the way it is stored and dispensed, and evidence of patient compliance to treatment

The Report indicated the total expenditure and number of patients and vials were underestimated at the time of listing. While there were limitations in interpreting the LSDP data, the Expert Panel noted it was unlikely there was use of eculizumab outside of the eligibility criteria.

Overall, patients appeared to be compliant with treatment. However, approximately one third of the patient cohort appeared to have had at least one break from treatment. The Expert Panel noted this may have been due to missing dispensing records or genuine breaks from therapy.

The Expert Panel reiterated its comments from ToR 2 and the need for the LSDP Guidelines to permit the use of doses above 900mg or a dosing interval +/- 14 days in cases of haemolysis.

There did not appear to be any issues with storage or dispensing of eculizumab.

Recommendation 7:

The Expert Panel noted that the utilisation of eculizumab had exceeded the initial estimates and advised that the risk share arrangement that is in place be reassessed.

ToR 7 – Investigate developing technologies that may impact future funded access

The Expert Panel noted that an alternative TGA-registered medicine (ravulizumab) was being considered for subsidy in Australia for PNH by the PBAC. Other competitors may enter the PNH market, and biosimilars of eculizumab were in development. These may impact the PNH market in terms of suitability of the disease and the medicines for the LSDP.

Post-Review update

The recommendations relating to eculizumab for the treatment of PNH will not be actioned by the LSDP. At the July 2021 PBAC meeting, ravulizumab (Ultomiris®) received a positive recommendation for the treatment of PNH. A medicine is ineligible for inclusion on the LSDP where an alternative is available on the PBS. Eculizumab for PNH was listed on the PBS on 1 March 2022. Access via the LSDP continued for a three-month transitional period until 1 June 2022 but was not available through the LSDP after this date.