

MEMORANDUM OF BOARD MEETING 2 DECEMBER 2013

To: PHARMAC Directors
From: Chief Executive
Date: November 2013

Proposal to decline the funding application for eculizumab (Soliris) in the treatment of paroxysmal nocturnal haemoglobinuria

Recommendations

It is recommended that having regard to the decision criteria set out in Section 2.2 of PHARMAC's Operating Policies and Procedures you:

resolve to decline the funding application from Alexion Pharmaceuticals, received in November 2011, to list eculizumab (Soliris) on the Pharmaceutical Schedule for the treatment of paroxysmal nocturnal haemoglobinuria;

resolve that the consultation on this proposal was appropriate, and no further consultation is required;

note the feedback from patients with paroxysmal nocturnal haemoglobinuria about the significant physical and mental impacts of the disease on their lives and their families; and

note that PHARMAC remains open to the possibility of revisiting the decision in the event of substantial changes to relevant factors such as the evidence of clinical benefits, price and funding availability.

Summary

- PNH is a rare blood disorder that affects approximately 60-70 patients in New Zealand to different extents of severity.
- Of those patients, approximately 12 to 20 would likely meet the criteria proposed by the Haematology Subcommittee of PTAC for treatment with eculizumab.
- We are aware of 8 patients who are currently seeking funding.
- Eculizumab (Soliris) is a monoclonal antibody that stops red blood cell destruction, which is characteristic of paroxysmal nocturnal haemoglobinuria (PNH).
- Eculizumab reduces the risk of blood clots occurring, which can be fatal and otherwise will have profound health impacts on patients wellbeing. Eculizumab can also reduce the symptoms associated with PNH such as fatigue and abdominal cramps.
- Eculizumab may extend overall survival although the extent is unclear from current evidence.
- This paper seeks the Board's approval of a recommendation to decline the funding application from Alexion Pharmaceuticals for eculizumab in the treatment of PNH.
- This proposal would mean that patients with PNH would continue not to have funded access to eculizumab. Patients would continue to receive the current treatments including anticoagulation, blood transfusions and regular clinical monitoring and review.
- Funding eculizumab would mean that other patients would miss out on treatments which are considered to offer greater overall benefits by PTAC (which recommended funding for eculizumab be declined), and which offer substantially more health gain for the funding (eculizumab is estimated to be associated with 0.4 to 0.9 Quality Adjusted Life Years gained per \$1 million invested).
- Based on current information the total funding that would be committed to an eculizumab funding decision would be approximately \$38 million over 5 years (NPV, 8% discount rate).
- The primary driver for the outcome of these evaluations is the very high price being sought by Alexion, which is around \$670,000 per patient per year.
- Lower prices are being charged overseas. However, even if those prices were obtained here, it would not alter the substance of our recommendation. These prices are still extreme relative to the expected benefits from eculizumab particularly when compared with other treatments, offering similar or greater benefits, to patients with other conditions.

Why Proposal Not Decided Under Delegated Authority

The proposal outlined in this paper has not been dealt with by the Chief Executive under delegated authority because:

- the estimated Financial Impact (NPV) of this proposal is more than \$10,000,000 of the Pharmaceutical Budget. The Financial Impact (NPV) is calculated on the basis of the net present value of the proposed subsidy (ex-manufacturer exclusive of GST) over 5 years at a discount rate of 8% to be paid by the funder for the product(s) and the forecast demand, taking into account any effect of the change /decision on that demand, versus the status quo; and
- the proposal is considered contentious by PHARMAC's Chief Executive because it is a proposal to decline the funding of a treatment, and in which there has been significant public interest.

The Proposal

We propose that the funding application for eculizumab (Soliris), for the treatment of PNH, from Alexion Pharmaceuticals be declined.

Estimate of the Effects of the Proposal

Clinical effects of this proposal

Current treatment in New Zealand for PNH aims to relieve symptoms and prevent serious clinical consequences, rather than effect a permanent cure. This includes blood transfusion to treat anaemia, immune suppression with corticosteroids to suppress ongoing red blood cell destruction, and anticoagulation with warfarin to prevent or treat blood clots. Stem cell transplantation is potentially a cure for PNH but it is associated with significant risks and is not the standard of care in New Zealand.

Eculizumab is not a cure for PNH either. It reduces the risk of blood clots caused by, and relieves the symptoms associated with, PNH (for example anaemia, fatigue and abdominal cramps) and it needs to be used for the rest of the patient's life.

The PTAC considered that there is excellent quality evidence that eculizumab reduces transfusion requirements, reduces haemolysis and improves haemoglobin levels, and the Committee considered that there was also good evidence that it reduces thrombosis rates and improves fatigue and quality of life. The PTAC considered that the extent of improvement in survival is uncertain from the current available clinical evidence, and its cost was very high. A summary of the PTAC's recommendations for eculizumab can be found in the next section of this paper and the full version of its minutes (and the minutes of the Haematology Subcommittee of PTAC) is attached in Appendix 1.

This proposal to decline the funding of eculizumab would mean that PNH patients in New Zealand would not obtain the clinical benefit from treatment with eculizumab detailed above. Patients would continue to receive the current standard of care of PNH in New Zealand including anticoagulation, blood transfusions and inpatient care when they develop complications.

In the 2012/13 financial year, PHARMAC spent \$17.5 million on new investments (new treatments and widening access to existing treatments) which benefited 52,400 patients. If the significant investment required to cover eculizumab treatment were made, it would mean funding would be unavailable for investment in other treatments which offer similar or greater health benefits, have higher PTAC priorities, or offer more health gain overall for patients who also have high health need.

We have heard directly from patients with PNH their stories about the significant impact of this disease on their life. We are mindful of this in making our recommendation, and also of PHARMAC's legislative objective and functions to consider all people who have need of pharmaceuticals and to provide funding from our limited means in a way that provides the best health outcomes, overall.

Cost-effectiveness

PHARMAC staff prepared a preliminary Technology Assessment Report (TAR) assessing the cost-effectiveness of eculizumab plus best supportive care compared with best supportive care in patients with PNH who meet the criteria proposed by the Haematology Subcommittee as defined below:

- 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 cost-utility analysis (CUA) range is estimated to be approximately 0.4 – 0.9 QALYs gained per \$1 million invested (\$1,100,000 – \$2,500,000 per QALY). This is based on incremental gains of 9.2 QALYs with incremental costs of \$11.4 million over a patient's lifetime. The full TAR is available in Appendix 2 (Technology Assessment Report No. 209: Preliminary Economic Analysis on eculizumab for paroxysmal nocturnal haemoglobinuria (PNH)).

This analysis models the cost-effectiveness of eculizumab for patients with PNH who meet the criteria outlined by the Haematology Subcommittee.

Patients currently receive blood and platelet transfusions as well as anticoagulants to try to reduce the risk of a thrombotic event and improve their health related quality of life. Although stem cell transplants can cure PNH, the mortality risk associated with the transplant is considered too great and most patients do not receive stem cell transplants.

At the price proposed by Alexion for eculizumab, the CUA result is not very sensitive to the other variables that are included in the model. Even with a 50% price reduction, this remains the case.

With a significant (>50%) price reduction we expect that the analytical model would become more sensitive to other variables such as:

- additional health states showing the deterioration over time in patients with PNH;
- proportion of patients who benefit from treatment with eculizumab;
- greater clarity regarding the quality of life of these patients;
- impact of adverse effects of eculizumab;
- the proportion of patients that are likely to receive benefit from eculizumab;
- possible long-term safety impacts of receiving eculizumab; and
- detailed costs and savings associated with blood transfusions and the infusion cost of eculizumab that are not currently included in the model.

Fiscal effects

This proposal to decline the funding of eculizumab in PNH would have no impact on the Combined Pharmaceutical Budget and DHBs.

The counterfactual (funding eculizumab as per Alexion's application, taking into account the Haematology Subcommittee's recommended criteria) would result in an approximate net cost of \$38 million (5-year NPV, 8% discount rate) to DHBs.

The table below summarises the calculations and assumptions behind these costs:

	2014	2015	2016	2017	2018	5- year NPV
New Zealand population	4,547,289	4,592,762	4,638,690	4,684,315	4,730,015	
Total PNH patients in NZ (Prevalence) ¹	72	73	74	74	75	
Patients with clinical symptoms and a clone size >50% ²	16	16	16	16	16	
PNH patients who would access eculizumab ³	12	13	13	14	16	
Net drug cost eculizumab⁴	\$8.0M	\$8.7M	\$8.7M	\$9.4M	\$11M	\$39M
Savings to DHBs through reduced PNH complications ⁵	\$0.12M	\$0.13M	\$0.13M	\$0.14M	\$0.16M	\$0.58M
Total net cost to DHBs	\$7.9M	\$8.6M	\$8.6M	\$9.2M	\$11M	\$38M

1. Prevalence of the PNH clone in general population of 15.9 per million (supplier submission and Hill et al 2006 (ASH Annual Meeting Abstracts; 108: Abstract 985))

2. 43% of patients with PNH would have a clone size >10% (supplier submission and Hill et al 2006 (ASH Annual Meeting Abstracts; 108: Abstract 985)). PTAC (March 2013) considered that restricting eculizumab to those with a clone size >50% would halve the patient number.

3. Uptake rates of 75% rising to 100% over 5 years.

4. Based on the commercial proposal from supplier dated March 18, 2013 with an effective net vial price of ██████ per 300mg vial which includes a ██████% confidential rebate. Dosing is 600mg weekly for 4 weeks, 900mg in week 5 and then 900mg fortnightly ongoing.

5. Estimated to be an average reduction of \$10,000 per patient per year from reduced hospitalisations for treatment of PNH complications which is consistent with supplier's funding application.

The number of patients who would be treated with eculizumab and, hence, the possible financial impact would depend on the access criteria. The cost per patient would, however, remain the same.

A comparison of international prices for eculizumab is outlined below:

Country	Source	Strength	Pack Size	Local Price	Exchange Rate	Price (\$NZ)
Proposal		300mg	1			████████*
United Kingdom	British National Formulary	300mg	1	£2800.00	0.5114	\$ 5475.17

Canada	Alberta Health	300mg	1	CAD 6742.50	0.8099	\$8325.10
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*This includes a [REDACTED] % confidential rebate.

Note: Prices are expressed ex manufacturer, excluding GST.

We note that the net pricing offered by Alexion is significantly higher than the public pricing for eculizumab in the United Kingdom. Alexion's legal representatives raised objections to PHARMAC's actions in disclosing this net pricing during the consultation process. Given that the net price offered by Alexion is significantly higher than the published pricing available in international markets and given arguments on the need for disclosure in view of the public interest, PHARMAC considers that there is no good reason to withhold this information.

PHARMAC Staff View

PHARMAC staff support this proposal.

During the consultation process, PHARMAC staff met with patients living with PNH, and their families and have heard, first-hand, the effects this disease has had on their health and quality of life. PHARMAC staff also met with a family member of a patient who is currently receiving eculizumab treatment free-of-charge from Alexion and heard feedback on the significant difference they consider eculizumab makes to [REDACTED] life. There is no doubt that PNH has significant impact on patients. Eculizumab would offer the opportunity for additional clinical benefit over the existing treatments that are funded.

The primary issue with eculizumab is its extremely high price. Secondly, although eculizumab has demonstrated clinical benefits on some important measures, the evidence for its long-term benefit on life expectancy is currently unavailable. These issues are relevant to both PHARMAC's budgetary impact and cost-effectiveness decision criteria.

Even assuming eculizumab was 100% effective, and guaranteed to restore patients to full health (which is not supported by the available evidence), it would still be about 20 times less cost effective than the average pharmaceutical funded by PHARMAC over the past two years. While cost-effectiveness is but one of PHARMAC's decision criteria, at this point it would seem unlikely that, in a counterfactual scenario, any benefits under the other decision criteria would counterbalance this.

A decision to decline funding for eculizumab would not mean the door is closed to eculizumab funding. PHARMAC could review this decision if material new information, for example new clinical evidence, or a new commercial proposal is received.

PTAC View

The PTAC first reviewed Alexion's funding application in February 2012. Its preliminary recommendation was to decline funding; however, it referred the application for advice from the Haematology Subcommittee of PTAC which met in August 2012. The Haematology Subcommittee recommended that eculizumab be funded, with low priority, subject to access criteria. The PTAC held a subsequent teleconference to discuss eculizumab in March 2013 and we note that three haematologists from the Haematology Subcommittee attended the teleconference at the invitation of the PTAC.

The minutes for the meetings are summarised below and the full versions are attached in Appendix 1:

PTAC February 2012

- The PTAC recommended that the application for eculizumab in PNH be declined.
- The Committee noted that the evidence for eculizumab was mainly from observational studies with only one randomised controlled trial, the TRIUMPH study (Hillmen et al. N Engl J Med. 2006; 355: 1233) which was not powered to detect differences in either thrombosis rates or mortality.
- 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.
- The Committee considered that there was an unmet clinical need for PNH treatments. The Committee considered that 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.

Haematology Subcommittee August 2012

- The Subcommittee recommended that the eculizumab be listed with a low priority subject to criteria limiting it to patients with 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 Subcommittee considered that the evidence available indicates that eculizumab is effective in reducing blood transfusion requirements and thrombosis rates.
- 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 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.
- The Subcommittee considered that there was 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.

PTAC March 2013

- After considering all the decision criteria, the Committee recommended that the application for eculizumab in PNH be declined on the basis of high cost per patient.
- Overall, the Committee considered that the quality of evidence to support that eculizumab reduced transfusion requirements, reduced haemolysis and improved haemoglobin levels, was excellent. The Committee considered that 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.

- The Committee considered that patients who were treated with eculizumab achieved improvements in their quality of life that were clinically important.
- 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 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 (Blood 2011; 117(25):6786) 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 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 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.

Comments from Interested Parties

Section 49(a) of the New Zealand Public Health and Disability Act 2000 (the Act) requires PHARMAC to consult, when it considers appropriate to do so, on matters that relate to the management of pharmaceutical expenditure with any sections of the public, groups or individuals that, in the view of PHARMAC, may be affected by decisions on those matters.

Accordingly, a consultation letter was circulated on 21 May 2013 to parties that, in the view of PHARMAC, may be affected by the recommendations contained in this paper.

The consultation letter, all responses received by 31 July 2013 and a summary of these responses are attached as Appendices 3, 4 and 5 respectively. We received 263 responses to consultation of which 8 were from clinicians, 15 were from patient support groups and 19 from PNH patients in New Zealand and overseas. The remaining 221 were from interested individuals. Of the 263 responses, 110 were from parties in New Zealand.

Summaries of what PHARMAC staff believe are the significant matters raised in these responses are provided below, each addressed in turn under the following headings:

- Quality of information provided by the consultation document
- Equity of access to treatment
- Special decision criteria required
- International funding of eculizumab

- Prioritisation of spending in New Zealand
- Suggested approaches to achieve funding for eculizumab
- Opportunity cost and fiscal risk
- Uncertainty of clinical benefit
- Role of the pharmaceutical industry

For the full response, please refer to Appendix 4.

Quality of information provided by the consultation document

Points made included:

- the number of PNH patients eligible for treatment with eculizumab was overstated, and consequently so was the cost of treating these patients and the effect on funding available for others.
- the pharmaceutical cost for eculizumab also did not take into account confidential rebates the supplier was willing to provide.
- it was unclear whether PHARMAC's cost analysis had taken full account of the costs to the public health system of PNH sufferers not receiving eculizumab and the loss of productivity to society.
- the statement about efficacy in the consultation document inadequately reflected how effective eculizumab is in treating PNH.
- the survival improvement for the treatment of PNH with eculizumab was understated.
- the above errors and omissions within the consultation document would have affected the consultation responses received and the consultation letter should therefore be withdrawn.

PHARMAC staff comment:

The patient numbers consulted on were based on the patient numbers estimated in Alexion's funding application and took into account the clinical advice we had received. A preliminary survey of New Zealand haematologists conducted by the Haematology Society of Australia and New Zealand (HSANZ) has highlighted that there are currently approximately 8-10 known patients with severe PNH in New Zealand. As eculizumab is taken long term, patient numbers would increase over time as newly diagnosed patients begin treatment or patients return from overseas.

The patient numbers would also vary depending on the actual access criteria but the high cost of treatment per patient and the cost-effectiveness of eculizumab would be unchanged by the patient number estimates and these remain key considerations.

The pharmaceutical cost consulted on was indeed net of rebates.

We highlighted in the consultation process that we did not at that time include the full account of the costs to the public health system of PNH sufferers not receiving eculizumab because although the complications associated with PNH were significant, the cost offsets from a reduction in those complications were very small relative to the acquisition cost of eculizumab (1.5% reduction in costs). PHARMAC does not currently take into account societal costs (i.e. lost productivity) when estimating the financial impact of all our funding

proposals (this is described in PHARMAC's policies/procedures for economic analysis¹). To do so would not make it more likely that all medicines would be funded. There may be consequences in terms of the mix of treatments ultimately funded, which may be more or less desirable, depending on one's point of view.

We consider that the information provided in the consultation was reasonable, based on the information available to us, and enabled people to form a view on the proposal and express that to us.

Some of the information provided involved assumptions, which is often the case and those assumptions took into account the clinical advice we had received.

Equity of access to treatment

- It was submitted that PHARMAC's proposal to decline funding for eculizumab breached the Human Rights Act 1993 which states, among other things, that it is unlawful to deny, or treat a person less favourably, on any of the prohibited grounds of discrimination. The submitter considered that PHARMAC's proposal would also be in breach of the Universal Declaration of Human Rights and the International Covenant on Economic, Social and Cultural Rights, to which agreements New Zealand is a signatory.
- One respondent also claimed that human rights impacts are a mandatory relevant consideration for all PHARMAC decisions, including the decision for eculizumab (see the New Zealand Organisation for Rare Disorders (NZORD) letter in Appendix 6).
- It was submitted that PHARMAC's proposal to decline funding contradicts a stated objective of the New Zealand Public Health and Disability Act 2000; that is, ensuring the best care and support of those in need of services. The submitter also considered the proposal to be contrary to the agreement between DHBs and PHARMAC about how funding decisions are made. This agreement has goals of 'equity of access, reducing inequalities and improving health outcomes for individuals and communities, which should guide the relationship and decision making.'
- A respondent claimed DHBs have a duty to address issues of rights, equity, fairness and community values. The submitters considered that PHARMAC is acting as the DHBs' purchasing agent and should use the same decision criteria and priorities that DHBs have – and not place so much emphasis on costs, cost-effectiveness and alternative use of the money.
- Some respondents contested PHARMAC's interpretation of several key phrases in its legislative brief, including the meaning of 'best health outcomes' and 'reasonably achievable'. Given that the words 'excluding those people with rare diseases' are not written anywhere, respondents had assumed that all New Zealanders' needs would be debated fairly and honestly.
- Some respondents felt PHARMAC has a social responsibility or moral obligation to help improve the quality of people's lives and where possible to improve their life expectancy.
- One clinician noted that in a country where a single DHB spends \$63 million on treatment of alcohol related harm, it is inappropriate to withhold treatment from a

¹ PHARMAC. Prescription for Pharmacoeconomic Analysis: methods for cost-utility analysis, Version 2.1 Wellington: PHARMAC, 2012. <http://www.pharmac.govt.nz/2012/06/26/PFFPAFinal.pdf>

small group of patients with very severe disease who have a significant chance of dying from it.

- Respondents stated that the role of ethics in decision making had not been addressed at all in this consultation (and had been poorly addressed by PHARMAC over many years). One respondent commented that ‘Appropriate and proper decision-making in health requires that these issues are more robustly addressed in a way that is consistent with the widely accepted role of ethics in healthcare in New Zealand.’

PHARMAC staff comment:

PHARMAC staff welcomed these submissions and took the opportunity to consider the alignment of PHARMAC’s processes with its human rights obligations and other legal requirements, including by seeking independent legal advice. PHARMAC staff acknowledge the fundamental importance of human rights, and note that the legal advice received indicates that under PHARMAC’s current approaches, these obligations are being met.

More information is provided under the legal advisor’s view.

Special decision criteria required

- Some respondents felt that PHARMAC should have special decision criteria for particularly high cost pharmaceuticals or treatments for rare diseases. Submitters noted that:
 - Patients suffering from rare diseases were considered to be doubly disadvantaged by 1) the higher cost of new treatments, and 2) the higher cost of a very small ‘market’ for that medicine.
 - The Ombudsman had considered that the decision criteria under the exceptional circumstances scheme ought to be clearly differentiated from those under the pharmaceutical schedule. According to one submitter ‘this opinion demonstrates the inappropriateness of considering medicines for individuals or tiny populations under the same criteria used for large populations’.
- It was noted that the wider health system in New Zealand has recognised the importance of very expensive treatment through its high cost treatment pool for high cost surgery, yet for some reason PHARMAC is yet to substantively address this issue.
- Submitters claimed that PHARMAC must amend its Operating Policies and Procedures (OPPs) to acknowledge the right of rare disease patients to access life restoring and lifesaving treatments as in the specific example of eculizumab.

PHARMAC staff comment:

We are currently in the process of reviewing our decision criteria as part of our broader OPP review. Relevant submissions in response to the eculizumab consultation will be considered as part of the decision criteria review.

The Ombudsman did not express a view as to whether PHARMAC should establish substantively different decision criteria in relation to its NPPA (Named Patient Pharmaceutical Assessment) scheme. Rather, his comments regarding the need to “differentiate” the criteria were a response to the fact that the NPPA policy incorporates the decision criteria without amendment, by reference to the OPPs.

PHARMAC does currently fund some high cost medicines. In the 2012/13 financial year, 85% of pharmaceutical spending was spent on 16% of patients. 29 patients received

pharmaceutical treatments that cost over \$100,000 (for the year). Five of these patients received approvals through the Named Patient Pharmaceutical Assessment (NPPA) policy, and the majority (24 patients) received treatments listed on the Pharmaceutical Schedule. The highest amount spent in 2012/13 on one patient (for one pharmaceutical) was approximately \$450,000².

Issues of ethics and the funding of high cost medicines are complex, as seen in extensive previous considerations of the issue^{3,4}.

International funding of eculizumab

- Some submitters noted that eculizumab is funded in up to 40 countries internationally, including many poorer nations.
- Many of the respondents making international comparisons stated that PNH patients were effectively obliged to emigrate or remain away from New Zealand.

PHARMAC staff comment:

We note and respect the fact that in some other countries a decision has been made to fund eculizumab. It does not necessarily follow that in the context of PHARMAC's particular obligations and approach to considering the funding of medicines, that the same outcome would be reached.

Prioritisation of spending in New Zealand

- It was argued that the public should be able to decide whether to spend more on "life saving" medicine or to put interest on student loans, or to raise taxes, or to stop wasting money on the military or movie productions.
- Some respondents considered PHARMAC should request further funds if its budget was inadequate to fund available treatments.

PHARMAC staff comment:

The current policy settings and legislative obligations require PHARMAC to gain the best health outcomes from pharmaceuticals, and to do that with the finite resource provided to it.

PHARMAC is engaged in an annual process for the establishment of its budget, including the provision of information and advice on the medicine investment options.

Suggested approaches to achieve funding for eculizumab

² Note that these figures are gross of confidential rebates

³ PHARMAC. How should high cost medicines be funded? Paper for public consultation, December 2006. <http://www.pharmac.govt.nz/2006/12/15/HCM.pdf>.

⁴ McCormack P, Quigley J, Paul Hansen P. Report to Minister of Health, Hon Tony Ryall: Review of Access to High-Cost, Highly Specialised Medicines in New Zealand. 31 March 2010. http://img.scoop.co.nz/media/pdfs/1005/Review_of_Access_to_High_Cost_Highly_Specialised_Medicines_31_April_2010.pdf

- It was submitted that PHARMAC should continue to negotiate with the supplier of eculizumab; respondents were of the view that Alexion would be prepared to enter negotiations with PHARMAC to lower the price of eculizumab. One clinician stated that the supplier had indicated to him that it would be able to provide a 50%-80% rebate on eculizumab.
- Respondents claimed that there are considerable financial risks involved in funding research and development of new treatments and therapies for rare diseases, and that the pharmaceutical industry cannot be expected to continually fund and support research into rare diseases when the government will not fund effective treatments using very shaky ethical grounds as its reason for refusal.
- Submitters noted that other countries have met the challenge of funding eculizumab by developing strict criteria to limit patients' eligibility. This was considered to be better than a 'no exceptions' rule.
- Some submitters considered that there was a need to introduce a part funding model where perhaps families, a DHB, government department or non-governmental organisation shared the cost.
- One of the groups in favour of PHARMAC's proposal to decline funding supported the establishment of a separate source of funding for patients with rare conditions who want access to medicines when the price is set very high.

PHARMAC staff comment:

When submitting funding applications, suppliers need to submit their best pricing possible as the PTAC and Subcommittees of PTAC take into account budget impact and cost-effectiveness when making their recommendations to PHARMAC. The supplier was made aware of the PTAC's concerns regarding the high cost of eculizumab when it reviewed eculizumab in February 2012 and the supplier had multiple opportunities to review its pricing after that. PHARMAC also highlighted to the supplier that it was welcome to submit an adjusted commercial proposal in response to PHARMAC's consultation to decline the funding of eculizumab in PNH. Such a proposal has not been received.

This proposal to decline the funding of eculizumab for PNH would not prevent PHARMAC from considering future commercial proposals from the supplier. However, substantial price reductions or other significant risk sharing approaches would be required. We have sought and received confirmation from the supplier that it had not indicated to any third party that it would be willing to consider a 50%-80% rebate on eculizumab and that it would not offer such a discount to PHARMAC.

Treatments for rare disorders are sometimes priced very highly. There are a range of perspectives on why this might be so.^{5 6} Regardless of the actual reason, PHARMAC is charged with obtaining the best health outcomes from within the resources made available to it. Where companies choose to price their medicines at levels that are significantly misaligned with the demonstrable benefit in comparison with competing medicines, this will impact on the likelihood of such treatments obtaining funding.

Targeting funding to certain indications, or segments of patient populations is a common approach for PHARMAC. The application from Alexion that is under consideration for decline is such a proposal for tight targeting, and which would not benefit from tightening further.

⁵ Light DW, Lexchin JR. Pharmaceutical research and development: what do we get for all that money? *BMJ*. 2012;345:e4348. doi: 10.1136/bmj.e4348. <http://www.bmj.com/content/345/bmj.e4348>

⁶ Melnikova I. Rare diseases and orphan drugs. *Nat Rev Drug Discov*. 2012;11(4):267-8. <http://dx.doi.org/10.1038/nrd3654>

It is not likely that part-funding eculizumab would lead to substantial benefits for patients, and this would conversely result in inequities in access to such funding.

Opportunity cost and fiscal risk

- Some responders agreed with the proposal to decline the funding of eculizumab because it was difficult to see, at the proposed price, how eculizumab would represent value for money.
- Submitters felt that, unless the price could be brought down, greater health benefits could be achieved for the New Zealand population by spending this money on other initiatives.
- It was argued that, although funding eculizumab for PNH may represent a small proportion of the pharmaceutical budget due to the rarity of the disease, a decision to do so would potentially set a precedent for other companies seeking funding for rare diseases treatments. Collectively, funding expensive rare disease treatments could have significant financial implications if the cost of treating each disease is similar to that of eculizumab in PNH.

PHARMAC staff comment: Submitters' points are noted.

Uncertainty of clinical benefit

- Submitters noted there was no new clinical evidence to support the claim that eculizumab returns life expectancy to expected norms.
- Respondents considered that, without the opportunity for independent scientific peer-review critique of all the findings, reliance on the evidence provided by the drug company of efficacy, safety, and long term benefit must be treated with caution. It was noted that key authors named on the published papers publicly available to date have all declared a conflict-of-interest association with Alexion Pharmaceuticals.
- A clinician noted that whilst other treatment options for PNH are limited, there are some beneficial therapeutic strategies for some patients.

PHARMAC staff comment: Submitters' points are noted.

Role of the pharmaceutical industry

- Two health interest groups expressed concerns about the growing potential for pharmaceutical companies to 'educate' patient groups and the public about treatment options as well as about particular drugs, and then claim to have brought an informed public alongside them.
- They were of the view that this unacceptable use of vulnerable people to publicly pressure governments and health agencies to fund expensive or over-priced new drugs must be exposed and rebutted wherever and whenever it occurs. Submitters noted Alexion Pharmaceuticals' funding for PNH patient support groups to be widely

recognised and the funding it has given to the New Zealand PNH support group is a matter of public record.

- Eculizumab was seen by these respondents as an extreme example of the pharmaceutical industry charging exorbitant prices for niche drugs and then 'vigorously' marketing these to the public.

PHARMAC staff comment: Submitters' points are noted.

Legal Advisors' View

[Redacted]

[Redacted]

[Redacted]

Implementation

Section 49(b) of the Act requires PHARMAC to take measures to inform the public, groups and individuals of PHARMAC's decisions concerning the Pharmaceutical Schedule. Accordingly, if the Board adopts the recommendations contained in this paper PHARMAC staff will take the measures outlined below to inform the public, groups and individuals of that decision. We recognise that, as a high-profile issue, this proposal is likely to draw public interest.

We are planning to issue the Board paper and the consultation responses received alongside the notification document. This will be preceded by a briefing to the Minister of Health and by information to the PTAC and the Haematology Subcommittee.

We intend to directly contact the relevant patient group to inform them of the decision.

The list of communications activities includes:

- Briefing to the Minister of Health
- Media statement for distribution
- Notification letter and associated information to PTAC/haematology subcommittee
- Direct contact with stakeholders, send notification letter and associated information:
 - PNH Support Association of New Zealand
 - Alexion Pharmaceuticals
 - Dr Humphrey Pullon
 - Dr Bartrum Baker, National Haematology Working Group
 - John Forman, New Zealand Organisation for Rare Disorders (NZORD)
 - Consultation respondents
- Web publish notification letter and associated information

Decision Criteria

Set out below is PHARMAC staff's assessment of the application of the decision criteria in section 2.2 of the Operating Policies and Procedures. This assessment is intended for discussion purposes, is not necessarily exhaustive and is not a substitute for the analysis contained in the paper. The Board is not bound to accept PHARMAC staff's assessment of the application under the decision criteria and may attribute different weightings to each of the criteria from those attributed by PHARMAC staff.

1. *The health needs of all eligible people within New Zealand;*
The health needs of patients with PNH are significant and would be unchanged as a result of this proposal. They would continue to receive other funded treatments or care currently available.
2. *The particular health needs of Maori and Pacific peoples;*
There is no evidence that PNH is more prevalent amongst Maori and Pacific peoples so this would be as above.
3. *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;*
There is currently no cure for PNH other than stem cell transplantation which is associated with significant risks. Patients would continue to receive supportive treatments like anticoagulation, hospital and specialist care for their condition.
4. *The clinical benefits and risks of pharmaceuticals;*
This proposal would result in no change to the clinical benefit and risks to patients when compared to status quo. Treatment with eculizumab would potentially result in reduced transfusion requirements, reduced haemolysis, improved haemoglobin levels, improved fatigue and quality of life, reduced thrombosis rates and prolonged survival. Treatment with eculizumab is also associated with an increased risk of meningococcal infections.
5. *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;*
The funding application for eculizumab in PNH is not cost-effective when compared with our other current funding options. Even when the life expectancy of patients who receive eculizumab was estimated to result in 'normal' life expectancy the CUA result was approximately 0.9 QALYs per \$1 million invested (\$1.2 million per QALY).
6. *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule;*
This proposal would have no budgetary impact to DHBs or the Pharmaceutical Schedule.
7. *The direct cost to health service users;*
Because eculizumab would remain unfunded with this proposal, patients would need to self-fund in order to access treatment with eculizumab.
8. *The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere; and*
No such objectives are relevant to assessing this proposal
9. *Such other criteria as PHARMAC thinks fit.*
No other criteria are relevant to assessing this proposal.