CHRONIC LYMPHOCYTIC LEUKAEMIA ADVOCATES NEW ZEALAND

12 September 2019

Mr Andrew Park
Therapeutic Group Manager
Pharmac
PO Box 10-254
WELLINGTON 6143

Email: consult@pharmac.govt.nz

Dear Mr Park

FEEDBACK ON PROPOSAL TO FUND VENETOCLAX FOR THE TREATMENT OF CLL

In summary, Pharmac is proposing that from 1 December 2019:

a. venetoclax would be funded, in combination with rituximab, for the treatment of CLL that has relapsed within 36 months of previous treatment

b. venetoclax would be funded as monotherapy for the treatment of previously untreated CLL with a specific genetic mutation (17p deletion or TP53 mutation).

1. MY REQUEST

I am writing on behalf of CLL patients to ask you to revise the above decision by funding ibrutinib as an essential treatment for CLL, in addition to venetoclax. While we welcome the fact that a new era treatment for CLL has at last been funded, we have serious concerns about the limitations of the chosen medicine and its inability to meet the needs of ***all*** CLL patients, in particular those with severe CLL.

2. BACKGROUND

I am a CLL patient whose life was saved five years ago by ibrutinib. My personal story can be found here. I am also a consultant physician, and I am founder and executive director of CLL Advocates NZ (CLLANZ), a patient advocate group for CLL. CLLANZ is a formal member of an international umbrella CLL advocates group, the CLL Advocates Network (CLLAN).

3. SUBMISSION TO THE HEALTH SELECT COMMITTEE

On 7 August this year I presented an oral submission to the Health Select Committee, following a written submission to the Committee (included as appendix to this document). This was in turn preceded by a petition to Parliament asking the Committee to urge Pharmac to fund ibrutininb and venetoclax for the treatment of advanced and poor prognosis CLL. My colleagues Dr Rob Weinkove, a leading New Zealand CLL specialist, and Dr Ben Schrader, a CLL patient and CLLANZ trustee also presented to the Committee.

Our main points were as follows:

a. Venetoclax is not a one-size-fits-all treatment. Both treatments are needed. Each works in a completely different way and both are needed for effective management of the spectrum of CLL. This reality is mandated in international treatment guidelines derived from evidence-based clinical data.

b. Ibrutinib and venetoclax are two new-era cancer drugs that enable a personalised approach to treatment and form part of a major innovation in cancer treatment. They have the potential to turn severe CLL into a manageable, asymptomatic disease rather than a fatal one. My colleague, Dr Schrader, and I are among many success stories as a consequence of this new era.

c. The subgroup of CLL patients with the most urgent and severe unmet needs is those with the chromosomal abnormality 17p deletion, who respond poorly to standard CLL treatment.

4. PHARMAC'S PROPOSAL

Our submission was presented on the basis that both ibrutinib and venetoclax are necessary and complementary, rather than interchangeable, and that both need to be funded, not one or the other.

Like me, my colleagues, fellow patients and their families are dismayed that only one has been chosen.

The flaws in this decision include that it:

a. seems to have been based purely on price (and a fixed, as yet unproven two-year treatment period), rather than efficacy based on durable clinical evidence

b. proposes that the 17p deletion group – those with the poorest prognosis – be treated with venetoclax as first line. There are no data for outcomes for first line treatment for this group and it is globally unregistered for this use. Neither patients nor clinicians can reasonably be expected to use an unregistered, unsubstantiated treatment

c. is likely to increase inequity of access to treatment for rural and Māori patients and those from low socio-economic communities, because of the complexity and potential complications of the administration of venetoclax and rituximab (with its mandatory hospitalisation). Improving equity of access, rather than reducing it, is a key focus of the Cancer Action Plan

d. fails to acknowledge the heterogenous nature of CLL that requires medication options with different modes of action, the quite different ways the two treatments work, and how they are recommended to be used in the spectrum of CLL patient scenarios. For example, 11q deletion, and high-risk Tumour Lysis Syndrome patients (bulky lymph nodes, high lymphocyte count and renal failure) should have ibrutinib, not venetoclax. The two treatments (ibrutinib and venetoclax) are not interchangeable; as well as working differently, they have quite different side effects and levels of tolerability for individual patients

e. contradicts international treatment guidelines for severe CLL where ibrutinib is universally the first choice medication

f. is in conflict with Pharmac's *own* insistence, reflected in previous funding decisions, on having mature data in a population consistent with the NZ patient populations. We note that:

- ibrutinib data are substantial and mature with over 6 years of follow-up in a population consistent with the NZ relapsed/refractory CLL patient population.

- data from the venetoclax Murano study are immature (3 years) and based on a population with only one prior treatment, which is not consistent with the NZ CLL patient population for whom venetoclax is proposed to be used, and

- there is a high degree of uncertainty in the clinical evidence as to the durability of treatment response to venetoclax in the Murano study.

5. SUMMARY

a. For a quarter to a third of CLL patients given venetoclax, the treatment will likely fail or not be tolerated. This will leave these patients with no other treatment options.

b. For treatment-naive patients with 17p deletion, the absence of data for the use of venetoclax compromises clinicians and patients.

c. The choice to fund venetoclax with rituximab will increase inequities of access for some groups of patients due to monitoring and hospitalisation requirements.

d. The complementarity of the two drugs is the key basis to recommending that both drugs be funded.

e. Pharmac's choice of only one of these treatments has been deeply disappointing for the CLL community, including clinicians, patients and their families.

f. In my own case, from day one of ibrutinib therapy, I've simply taken the same dose of tablets each morning, enabling me to continue with my active, productive life. This is in marked contrast to the likely impact and significant disruption that treatment with venetoclax and rituximab would have had on my life.

Yours sincerely

Neil Graham FRACP, FRCP
Founder & Executive Director
CLL Advocates New Zealand
www.clladvocates.nz

APPENDIX

Submission to the Health Select Committee

on the

Funding of life saving medicines ibrutinib and venetoclax

for Chronic Lymphocytic Leukaemia (CLL)

20 June 2019

Introduction

This submission has been prepared by Neil Graham, founding executive director of CLLANZ (Chronic Lymphocytic Leukaemia Advocates New Zealand), a recently launched patient support group for people with CLL. I am also a Consultant Physician and I am living with CLL.

The submission includes the following appendices:

1. About CLL
2. International guidelines summary for use of ibrutinib and venetoclax for CLL
3. CLL therapies in New Zealand
4. Treatment outcomes observed with ibrutinib and venetoclax
5. Five patient stories

I wish to appear before the committee in support of my submission.

Submission

That the Health Select Committee:

1. **Urges PHARMAC to fund the Medsafe-approved medications ibrutinib and venetoclax** for all appropriate CLL patients, particularly the following 'high-need' subgroups who present an urgent unmet need:
   i. Patients with relapsed or refractory disease (i.e., CLL that has returned after a period of responding to treatment, or is no longer responding to chemotherapy);
   ii. Patients with 17p deletion/TP53 chromosomal abnormality, a poor prognosis subgroup of CLL;
   iii. Patients who are less able to tolerate cytotoxic chemotherapies[1] due to older age and other medical conditions

   and/or to urgently and publicly explain its rationale for further delaying funding these desperately-needed medicines.

2. **Recommends to Parliament that a review be undertaken as a matter of urgency of PHARMAC's processes and operating model in regard to modern oncological medications**:
   i. Including a specific review of PHARMAC's statutory objective:

[1] Medicines that are toxic to living cells, including cancer cells - fludarabine and cyclophosphamide are examples used in CLL.

"to secure for eligible people in need of pharmaceuticals the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided."

ii. Is this objective still applicable in today's radically different pharmaceutical environment?

iii. How does PHARMAC measure success and optimal health outcomes and how does it weigh the value of individual lives?

iv. How does PHARMAC ensure 'equity of access' to healthcare?

3. **Recommends to Parliament that a pilot rapid access solution for modern oncological medications be developed and put in place as a matter of high priority, that**

   i. Takes a risk-sharing and cost-sharing approach to negotiation with drug companies, including provisional funding only, initially, with analysis of effectiveness at the end of the provisional period.

   ii. Applies a public ICER (incremental cost-effectiveness ratio) threshold to all these medications to enable PHARMAC to achieve the best possible price for New Zealanders sooner/faster.

   iii. Adopts an analogous model to those operating well in countries like the UK, Canada and Australia, where many more modern oncological medications are funded, faster.

4. **Recommends to the Government and commends to the Parliament an immediate increase in PHARMAC's medications budget to bring it into line with other OECD countries**.

   i. Increase NZ's current allocation for medications of only 5% of the national health budget to be aligned with the OECD average of at least 10%, and

   ii. Makes this judgement and allocation in the light of budget currently allocated to preventing the loss of and saving the lives of people involved in accidents.

Overview

- I am alive and well, working as a physician, teaching, paying taxes, and enjoying all that life has to offer, because I was able to access one of these drugs. If not, I would have been dead 5 years ago.

- Not since the introduction of antibiotics almost a century ago has the world seen such death-defying therapeutics development as we are seeing now in cancer. The introduction of drugs like ibrutinib and venetoclax for CLL treatment are only two examples of many many life-changing innovations.

- The PHARMAC model (now 20 years old) of 'delaying while bargaining the price down' worked well in the early years but it is no longer fit for purpose. It does not and cannot work for revolutionary, life-saving treatments that are streaming onto the market for people in life and death situations

- It must change or it must be modified by adding a rapid access scheme, of which there are many models working in the Western world. Some of these include the ability to share the risk and cost with the pharmaceutical company's and divest if the drug does not measure up to expectations.

- PHARMAC is ignoring recommendations published in international guidelines for CLL treatment. In particular, international recommendations for patients with a specific chromosome abnormality, 17p deletion, or relapsed/refractory disease seem to have been entirely disregarded. These patients have an

urgent unmet need: chemotherapy is unlikely to work for them, but ibrutinib and venetoclax are highly effective, and would afford an excellent prognosis.

- Ibrutinib and venetoclax have been shown to have a superior effect in patients in the high need subgroups of CLL described earlier. They both have high response rates and an enduring therapeutic effect. Ibrutinib and venetoclax are also relatively free of important side effects and both are oral medications, making for convenient treatment without substantial burden on healthcare resources.

- What price are we putting on a life? Please read the patient stories appended to this submission, all people leading productive lives who would all be dead or seriously sick if not for these modern drugs.

  Audrey accessed venetoclax through a clinical trial. She feels she has been given a new gift of life. She is in remission and has resumed working and leading an active life.

  Ian was able to start ibrutinib through a compassionate access programme following several years of illness and a precarious state of health. He has seen a dramatic difference to his life, with only minor side effects. He works full-time, exercises and is happy.

  Ben received treatment with ibrutinib, also through a compassionate access programme. Previously his CLL had been treated but relapsed twice. He has had no discernible side effects with ibrutinib and says without it his CLL would have returned. He feels great, is able to work and be there for his family and friends. Getting CLL is a case of bad luck but access to ibrutinib shouldn't' be left to chance.

  Graham has the high-risk deletion of the 17p chromosome, meaning his CLL is harder to treat. He describes treatment with a novel agent via a clinical trial as his "Lazarus experience", bringing him back from the near-dead. Graham's NZ born brother is an Australian citizen and would have received ibrutinib for about $40 a month if he'd been the one diagnosed with del17p CLL, while in NZ if you aren't lucky enough to be accepted onto a clinical trial or rich enough to pay you can only expect a place on death row.

- New Zealanders are dying unnecessarily, whilst the rest of the OECD has largely embraced these and many other modern oncological medications. It is a national disgrace and must change.

Ibrutinib and venetoclax should be funded for the following reasons:

1. CLL patients in the high-need subgroups outlined above lack appropriate therapy

- Current publicly funded treatments for the subgroups of high-need CLL patients described are limited by toxicity. For example, fludarabine, a chemotherapy used in the funded FCR regimen Is recommended by guidelines not to be given to patients over 70 years of age due to toxicity concerns (1). With the majority of CLL patients aged 65 years or more (2), use of fludarabine based regimens is limited.

- A subset of patients may achieve durable remissions with other treatments; however, most will relapse within a few years and therefore require alternative treatments to achieve a response to therapy (3).

- With a lack of options for patients who relapse, or become refractory to current treatments, there exists a substantial unmet clinical need for effective and well tolerated therapies for the high-need subgroups (i.e., del17p, relapsed/refractory) of CLL patients in New Zealand.

2. *International guidelines for CLL treatment consistently recommend ibrutinib and venetoclax based on the body of clinical evidence for each*

- Whilst there are no specific CLL guidelines developed in New Zealand, experts in CLL refer to international evidence based and peer reviewed guidelines. These international guidelines are created, reviewed and updated in alignment with clinical evidence published in peer reviewed journals. This is typically the same evidence provided to PHARMAC in funding submissions for new therapies (i.e., high quality randomised controlled trials).

- Examples of recommendations from the National Comprehensive Cancer Network (NCCN) (1); the European Society of Medical Oncologists (ESMO) (4); and the British Society for Haematology (BSH) (5) include:

    - *In first-line therapy, ibrutinib is the preferred treatment option for frail patients with significant comorbidities (NCCN);*
    - *Ibrutinib and venetoclax are included as preferred options for patients with relapsed or refractory disease, regardless of their age and comorbidities (NCCN);*
    - *Ibrutinib is the preferred treatment option for first-line therapy of patients with del17p (NCCN);*
    - *In relapsed/refractory patients with CLL and del17p, ibrutinib monotherapy, venetoclax plus rituximab and venetoclax monotherapy are listed as preferred regimens (NCCN);*
    - *Ibrutinib is the treatment of choice in front-line therapy for patients with TP53 disruption (del17p) (BSH);*
    - *Ibrutinib monotherapy is a treatment of choice for patients with CLL who are refractory to chemoimmunotherapy, have relapsed after chemoimmunotherapy, or for whom re-treatment with chemoimmunotherapy is inappropriate (BSH);*
    - *Venetoclax is the treatment of choice for patients who fail BCR inhibitor therapy (BSH);*
    - *It is recommended that patients with TP53 mutation/del17p are treated with ibrutinib in front-line (ESMO);*
    - *Patients unsuitable for BCR inhibitor therapy may be treated with the BCL2 inhibitor venetoclax (ESMO);*
    - *If relapse occurs within 24-36 months after chemoimmunotherapy, or if the disease does not respond to any first-line therapy, the therapeutic regimen should be changed. Treatment options include ibrutinib, and if the patient failed BCR inhibitor therapy, venetoclax (ESMO).*

- These examples represent the subgroup of high-need CLL patients described earlier. Many guidelines also recommend the use of targeted therapies in other subgroups of CLL. This submission, however, has focussed on those at greatest need of new therapy options in New Zealand.

3. *PHARMAC's own clinical advisory committees have recommended ibrutinib and venetoclax be funded with medium to high priority based on the available clinical evidence*

- Ibrutinib has been recommended for funding and prioritised in 2016, however remains unfunded. Venetoclax has been recommended for funding and is undergoing assessment for prioritisation.

- A summary of the evidence for ibrutinib and venetoclax from clinical trials in the high-need CLL patients is provided in appendix 4. Key findings include:

    - *Ibrutinib significantly reduces the risk of death or disease progression by 87% compared with ofatumumab in patients with relapsed/refractory CLL (p<0.0001) (6);*
    - *With up to 7 years follow-up, the estimated overall survival rate for relapsed/refractory patients treated with ibrutinib is 52% (7);*
    - *91% of patients with relapsed/refractory CLL who had progressed on ibrutinib and were then treated with ibrutinib were still alive at 12 months with follow-up ongoing (8);*
    - *Venetoclax + rituximab significantly reduces the risk of death or disease progression by 84% compared to bendamustine + rituximab in patients with relapsed/refractory CLL (p<0.001) (9);*
    - *With up to 7 years follow-up, median overall survival is 57 months for ibrutinib treated patients with relapsed/refractory del17p CLL (7);*
    - *The estimated survival rate at 5-years for front-line ibrutinib treatment of del17p CLL is 85% (3);*
    - *Venetoclax + rituximab reduced the risk of death or disease progression by 87% compared with bendamustine + rituximab at 2 years follow-up (10);*
    - *The estimated rate of overall survival at 2 years is 73% for venetoclax treated patients with relapsed/refractory del17p patients (11).*

- These targeted treatments are changing outcomes for the better around the world, in New Zealand, however, they remain frustratingly out of reach for the people who need them.

4. ***New Zealanders with high-need CLL have been failed by the existing economic model of medication access***

    - Highly effective treatments for people with CLL are ready and waiting to be made available to the New Zealanders who desperately need them; however, they're stuck in a waiting game, despite PHARMAC's own committees recommending they be funded.

    - With a lack of public funding, people are dying of CLL who would have survived if they lived in Australia, or other countries, where these medications are funded.

    - In appendix 5 of this submission there are several stories of New Zealanders who have been failed by the public funding system, however, they've accessed ibrutinib and venetoclax on compassionate grounds or within a clinical trial. Without this access they may not have been alive today to share their stories.

    - Relying on compassionate access, self-funding or a clinical trial is neither sustainable nor acceptable. Self-fund and you live, can't afford to and you die represents a model in crisis.

Recommendations

Submission

That the Health Select Committee:

5. **Urges PHARMAC to fund the Medsafe-approved medications ibrutinib and venetoclax** for all appropriate CLL patients, particularly the following 'high-need' subgroups:
   iv. Patients with relapsed or refractory disease (i.e., CLL that has returned after a period of responding to treatment, or is no longer responding to treatment);
   v. Patients with 17p deletion/TP53 chromosomal abnormality, a poor prognosis subgroup of CLL;
   vi. Patients older than 70 who need treatment, but who generally are unable to tolerate conventional cytotoxic chemotherapy (i.e., medicines that are toxic to living cells, including cancer cells - fludarabine and cyclophosphamide are examples used in CLL).

   and/or to urgently and publicly explain its rationale for further delaying funding these desperately-needed medicines;

6. **Recommends to Parliament that a review be undertaken as a matter of urgency of PHARMAC's processes and operating model in regard to modern oncological medications**:
   v. Including a specific review of PHARMAC's statutory objective:
   "*to secure for eligible people in need of pharmaceuticals the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided.*"
   vi. Is this objective still applicable in today's radically different pharmaceutical environment?
   vii. How does PHARMAC measure success and optimal health outcomes and how does it weigh the value of individual lives?
   viii. How does PHARMAC ensure 'equity of access' to healthcare?

7. **Recommends to Parliament that a pilot rapid access solution for modern oncological medications be developed and put in place as a matter of high priority, that**
   iv. Takes a risk-sharing and cost-sharing approach to negotiation with drug companies, including provisional funding only, initially, with analysis of effectiveness at the end of the provisional period.
   v. Applies a public ICER (incremental cost-effectiveness ratio) threshold to all these medications to enable PHARMAC to achieve the best possible price for New Zealanders sooner/faster.
   vi. Adopts an analogous model to those operating well in countries like the UK, Canada and Australia, where many more modern oncological medications are funded, faster.

8. **Recommends to the Government and commends to the Parliament an immediate increase in PHARMAC's medications budget to bring it into line with other OECD countries**.
   iii. Increase NZ's current allocation for medications of only 5% of the national health budget to be aligned with the OECD average of at least 10%, and

iv. Makes this judgement and allocation in the light of budget currently allocated to preventing the loss of and saving the lives of people involved in accidents.

Summary

Internationally accepted guidelines for CLL treatment cannot be followed in New Zealand because PHARMAC does not fund the required treatments.

New Zealanders are dying because of inability to fund these life-saving therapies in CLL. This does not happen in other western countries, because of these medications being funded by public health services.

New Zealand should adopt funding and supply models of countries like Australia, where more cancer medications are publicly funded and available. This is reflected in cancer treatment outcomes when comparing the two countries.

The world will look at New Zealand as a first world country with third world outcomes in oncological therapeutics, once the success story of modern oncology evolves further.

A national revolution in this public health issue is gaining momentum and will continue. PHARMAC's stance and the outcomes in cancer will not be tolerated.

Providing funding for ibrutinib and venetoclax is urgent and essential for New Zealanders with high-need CLL.

Background to this submission

Ibrutinib was first registered by Medsafe in New Zealand in 2015 and subsequently prioritised for funding by PHARMAC in 2016. Venetoclax was registered in 2017 and has also been prioritisation for funding. PTAC have requested further advice from CaTSoP on the relative priority of both. Both are targeted treatments for CLL proven to increase survival without the need for the addition of toxic chemotherapy and both remain unfunded in New Zealand.

Ibrutinib and venetoclax are recommended by international guidelines as preferred treatments for CLL patients with del17p, patients with relapsed/refractory disease and for patients unable tolerate chemotherapy (1, 4, 5). Both are widely funded in other OECD countries, including Australia.

These two medications have been shown to have a superior effect in patients in the high need subgroups of CLL described earlier. They both have high response rates and an enduring therapeutic effect. For example, 5 years post diagnosis, 85% of CLL patients with del17p treated first line with ibrutinib and 54% of CLL patients with del17p treated at relapse are still alive (3). Ibrutinib and venetoclax are also relatively free of important side effects and both are oral medications, making for convenient treatment without substantial burden on healthcare resources (6, 9).

The economic model of medication access in New Zealand for modern oncological medications seems to be self-fund and you live, can't afford to and you die. The lack of funding means people are dying of CLL who would have survived had they lived in Australia. In appendix 5 of this submission there are five stories of New Zealanders who have accessed ibrutinib, venetoclax and other novel treatments on compassionate grounds. These people are well, working, and enjoying life. Without access to the novel treatments that they received on compassion grounds or via clinical trials many would not be alive to share their stories.

Most New Zealanders can't afford to self-fund their cancer medication. Unless they can generate community or compassionate funding or become part of a drug trial (often difficult because of exclusion criteria), they are left with treatment unlikely to work, or no treatment, and death. Whilst this happens, the people of many other OECD countries, where these drugs are funded, reap the benefits of increased survival.

PHARMAC, in its two plus decades of existence has rightly received global acknowledgment for initiatives to improve value for money for New Zealand's drug budget. Their response to therapeutic innovations in cancer, however, has been anachronistic. Not since the introduction of antibiotics almost a century ago has the world seen such death-defying therapeutics development as we are seeing now in cancer. PHARMAC has responded with a strategy of rationing by delay. They ask for more statistical data, when many other countries' public funding-equivalents have accepted the data and conclusions as valid in cancer survival studies.

High-profile guidelines written by international experts in CLL are developed, peer-reviewed and updated based on available clinical evidence. Strong recommendations are made for ibrutinib and venetoclax use, particularly in patients with del17p and for patients with relapsed/refractory CLL (see appendix 2) (1, 4, 5). International guidelines state that FCR has no place in the management of del17p because of such poor response rates (1). Ibrutinib and venetoclax are consistently recommended. How PHARMAC can fly in the face of international expert opinion is hard to rationalise.

With the current model and budget, PHARMAC do not fund these medications. New Zealanders are dying unnecessarily, whilst the rest of the OECD has largely embraced modern oncological medications. It is a national disgrace and must change.

ABBREVIATIONS

BCR	B-cell receptor
BCL2	B-cell lymphphoma-2
BR	Bendamustine plus rituximab
BSH	British Society for Haematology
BTK	Bruton's tyrosine kinase (BTK is a BCR-associated enzyme, ibrutinib inhibits BTK)
CaTSoP	Cancer Treatments Subcommittee of PTAC
Chemoimmunotherapy	Combination of chemotherapy with a monoclonal antibody
CLL	Chronic lymphocytic leukaemia
CLLANZ	Chronic Lymphocytic Leukaemia Advocates New Zealand
del17p	Deletion of 17p (chromosomal abnormality, typically signalling poor prognosis in CLL)
ESMO	European Society for Medical Oncology
ITP	Immune thrombocytopenia
ICER	Incremental Cost Effectiveness Ratio
FCR	Fludarabine plus cyclophosphamide plus rituximab
MAB	Monoclonal antibody
NCCN	National Comprehensive Cancer Network
PI3K	Phosphoinositide 3-kinase
PTAC	Pharmacology and Therapeutics Advisory Committee
QALY	Quality adjusted life years