July 31, 2020

On behalf of the members of Chronic Lymphocytic Leukemia Patient Advocacy Group (CLLPAG) and as part of the consultations surrounding the PMPRB Draft Guidelines, we would like to submit our comments on the proposed changes to the method by which the PMPRB regulates the price of medicines in Canada.

1 Introduction

The CLL Patient Advocacy Group is a volunteer organization representing Chronic Lymphocytic Leukemia patients with 300 members across Canada.

Our mission is advocate and provide education to improve access to health care that will extend the lives of Canadians affected by Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL).

Among our activities, we participate in the CADTH and INESSS drug reimbursement review processes by providing the patient and caregiver perspective of what it is like to live with, and be treated for, CLL & SLL. We also organize CLL Live – a renowned free educational conference for patients and caregivers featuring talks by leading specialists from Canada, the US and Europe.

2 CLL patients have benefited from innovative treatments

Our view of the proposed PMPRB guidelines has been shaped by the remarkable evolution of CLL treatments in the past 15 years. If one of the functions of the current pricing system is to encourage the development of effective treatments for disease, it has certainly worked well for CLL patients. Notable developments of the past 15 years include:

- The addition of monoclonal antibodies to chemotherapy has given lasting remissions to a subset of CLL patients whose IGHV gene in cancerous cells is mutated (more than 15 years for the patients first treated).
- The introduction of a BTK inhibitor drug has given remissions of up to 8 years, to date, to many patients who either have relapsed after chemoimmunotherapy or whose genetic profile makes the latter treatment ineffective.
- For patients who suffer from side effects from the BTK inhibitor, an alternative is now available in the form of a second drug of this type with fewer side effects.
- Another new drug, a BCL-2 inhibitor, has also proven to be effective against CLL.

Research to improve CLL treatment is ongoing:

- Time limited treatment strategies as an alternative to BTK inhibitors, which need to be taken for the life of the patient. Will the
administration of a BCL-2 inhibitor for a limited period of 2 years, alone or in combination with other drugs, provide a lasting remission?

- Different combinations of CLL drugs are being tested.
- CAR-T treatments are under development and have shown some effectiveness against CLL.

Treatments developed in the last 15 years have extended patients’ lives by many years and have given them a good quality of life. Research is ongoing on time limited treatments and for a cure, both of which promise to reduce the overall cost of treatment compared to taking a BTK inhibitor daily for life.

A recent overview of CLL in the New England Journal of Medicine\(^1\) concluded:

“Clearly, the new agents have already improved the prognosis and quality of life for many patients with CLL, especially those with high-risk CLL. The challenge for this new decade is to capitalize on the early success of the novel agents with regimens that reduce the duration of drug exposure and the associated risks of toxic effects and resistance, as well as treatment costs. (Emphasis added)”

Despite all these developments, a cure for CLL is still elusive. Fear of a relapse is the sword of Damocles hanging over the heads of CLL patients in remission.

### 3 Comments on the PMPRB presentations

We have seen the PMPRB presentations regarding the relationship between drug prices and clinical trials as well as drug prices and drug introductions. While these presentations were informative, they did not alleviate many of our concerns.

#### 3.1 What is the real premium paid for medicines in Canada? The PMPRB’s case rests on comparisons of list prices, not the real prices paid.

The PMPRB presentation to stakeholders\(^2\) compares the price of drugs in Canada versus those of other countries in order to demonstrate that Canada pays higher prices for drugs and that there is no relationship between prices and drug introductions as well as prices and clinical trials.

We assume that these comparisons are based on list prices, since the actual prices paid (the rebated price) are not known in most cases. A comparison based on the real prices might well lead to a different conclusion.

As a patient group, we are in no position to have an informed opinion on the prices paid in Canada relative to those of other countries. We only note that we are not completely convinced by the case presented by the PMPRB.

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\(^2\) Revised PMPRB Guidelines, Overview of key changes, July 8, 2020, Public Webinar.
3.2 Patients are particularly concerned by phase 3 clinical trials

The PMPRB webinar on pharmaceutical R&D makes the case on page 17 that “A minority of new clinical trials in Canada are funded by patentees”. We would like to point out that the clinical trials of greatest interest to patients are the phase 3 trials, because these trials accept a greater number of participants and are therefore more accessible. According to the presentation, more than half (55%) of phase 3 trials are funded by patentees.

We remain concerned about a reduction in the number of clinical trials in Canada, particularly the phase 3 trials.

3.3 Patient support programs could be compromised.

A topic that PMPRB did not discuss in its presentations is the availability of support programs offered free of charge to patients by pharmaceutical companies. As we understand it, the provision of the programs is currently part of the price negotiations undertaken between manufacturers and the pCPA.

The patient support programs offer personalized support. They are not meant to replace healthcare providers or patient support groups but rather complement what they already offer and provide further support.

Patient support programs provide written and phone support from a specialized nurse to answer patient questions about the medicine or to assist patients when they experience side effects. Being specialized in patient support, the nurses that provide this service have in-depth knowledge of the particularities of the drug and its side effects. The provision of a 1-800 telephone number ensures that patient support programs are more easily accessible to patients than the hospital or doctor’s office.

Patient support programs also provide support in dealing with the complexities of obtaining coverage from private insurance companies. A CLL patient described his experience as follows:

"We have extended insurance and are covered for catastrophic drug costs. Nevertheless, I spent a few stressful weeks awaiting the company’s official agreement to cover the cost of the drug. The drug company’s patient support program took over the task of seeing that my oncologist prepared answers to the questions posed by the insurance company and relayed the completed paperwork to the insurance company and the hospital’s pharmacy. When the insurance company initially delayed their agreement, the drug company’s reimbursement specialist called me several times and assured me that the first month’s drug supply would be given to me at no charge. He also told me that, should the insurance company for some reason refuse to pay, the drug company would continue supplying me with the...

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3 Drug pricing and its impact on R&D investments, clinical trials and availability of medicines in Canada, PMPRB July 6, 2020
drug. The insurance company eventually did agree to pay. I can only express my gratitude to that drug company.”

The PMPRB proposals do not take into account cost of providing these programs is when setting the price of medicines, leading us to fear that they will no longer be offered by pharmaceutical companies whose prices are set under the guidelines.

4 The cost of pharmaceuticals must be addressed, but not at the expense of patients

The pharmaceutical industry, as it currently functions, has worked for CLL patients in Canada and around the world. This despite its problems, amply documented and that we do not dispute.

One of these problems is cost. The novel treatments outlined above are expensive and the price for each new treatment seems higher than the previous one. They are no doubt part of the high cost drugs category under the PMPRB guidelines.

While it is the mission of the PMPRB to control the cost of pharmaceuticals, this must not be done at the expense of patients.

Along with many other patient groups, we are concerned that magnitude of the price reductions and the uncertainty in the determination of those prices will result in fewer innovative treatments being introduced to Canada.

4.1 The PMPRB is solely focused on maximizing price reductions to the exclusion of other considerations.

While the mandate of the PMPRB “ensures that the prices of patented medicines sold in Canada are not excessive”, it is not at all clear what makes a price “excessive”. Put differently, nothing in what we have seen in the PMPRB proposals sets out the parameters of what would be a “fair price”, taking into account the factors of affordability, return on investment, incentives for innovation, etc.

Admittedly, this is a vastly complicated question. Nonetheless, it has received attention at the international level by the WHO. We believe that the PMPRB should have provided a policy framework to guide the formulation and application of its guidelines.

It is our impression that the objective of the PMPRB is to lower prices the maximum amount possible, with no reference to other public policy objectives such as those enumerated by the WHO:

- Equitable and timely access: patients in need should have access to cancer medicines in a fair and timely manner without compromising the quality and safety of medicines.
- Affordable access: patients should be able to afford cancer medicines over the full course of treatment.

• Health system sustainability: spending on cancer medicines should not divert resources away from the provision of other essential health products and services.

• Good governance: pricing and procurement process should observe the principles of transparency, efficiency and accountability.

• Balanced incentives: policies should align its intended objectives with the goals of different stakeholders, which may include appropriate prescribing and dispensing, R&D and industry development.

In the absence of policy framework balancing the different parameters regarding the fair pricing of pharmaceuticals, we remain concerned that the single focus on lowering prices to the exclusion of other considerations will result in prices that are so low that fewer innovative medicines will be introduced to Canada.

4.2 It’s not just the price, it’s the unpredictability of the price setting process that will stymie the introduction of innovative medicines to Canada

Two important characteristics of an effective regulatory scheme are certainty and transparency. Those being regulated, as well as other stakeholders, must be able to predict with reasonable certainty the outcome of the regulatory process.

For a business uncertainty with regard to the outcome of a regulatory process increases the probability of making a bad, and costly, decision. Alternatively, where the issues are complex, there must be some room for negotiation between the regulators and business, allowing the exchange of information about the particularities of the situation and giving business some confidence it can influence the outcome.

A WHO report on the pricing of cancer medicines reviews mechanisms used by payers worldwide to control prices. These mechanisms are transparent and predictable and/or they leave room for negotiation between the manufacturer and the government. A manufacturer is able to predict the outcome with reasonable certainty or, in the case of negotiation, is able to exercise some control over it.

The use of external reference pricing (PMPRB 11) meets the tests of predictability and transparency. However, the methodology proposed to use the pharmacoeconomic factors to set the maximum rebated price does not.

For a company (indeed for any organization), there comes a point where the uncertainty is simply too great to proceed with a project, such as the introduction of a medicine to a new market. This is what we fear with the proposed method of using ICER in setting the price of a medicine.

5 Using a single value ICER is a misuse of pharmacoeconomic analysis

CLLPAG has participated in 10 reimbursement evaluations by CADTH and INESS for different medicines for CLL. We support the process used by these organizations

and the way they use pharmacoeconomic analysis to inform decisions taken by expert committees with input from stakeholders, i.e., patient groups and clinicians.

Pharmacoeconomic analysis has value in organizing the relevant information, making explicit assumptions used in the analysis and clarifying data quality and data gaps. When combined with human judgement and stakeholder input, this kind of analysis is an important part of the decision making process.

5.1 Many value judgement are involved in the determination of an ICER, it is not an objective number.

We believe it is a misuse of pharmacoeconomic analysis when the result is boiled down to one number, shorn of all caveats and used without human judgement to decide a price which will determine whether a treatment is introduced to Canada or not (as per the decision of the manufacturer to accept or not the maximum rebated price). There are so many value judgements involved in the analysis and its interpretation that a single value ICER can never be an objective measure of value.

To take but one example: as we understand it, the usual time horizon for an analysis is five years, much shorter than the time horizon for a cancer patient diagnosed in his or her fifties, sixties or even seventies. How then will a single ICER value take into account the potential of a treatment to give a remission that will last more than 5 years? An expert committee will stakeholder input can evaluate this possibility, despite the absence of overall survival data, if a surrogate end point indicates such a potential.

In the case of CLL, a one time or time limited treatment that produces a lasting remission is both better for the patient and cheaper for the health system when compared with a medicine which must be taken daily for life. Both are novel treatments, both are expensive, but one is less expensive over the lifetime of the patient.

The choice of time horizon is but one example of the assumptions built into the ICER that require human judgement and stakeholder input to properly evaluate. A more complete analysis of these limitations can be found in a White Paper by the Office of Health Economics in the UK “Are Cost Effectiveness Thresholds Fit for Purpose for Real World Decision Making”.

5.1.1 The process for determining the value of the ICER that will be used to determine the price is unknown.

The ICER that is calculated by the pharmacoeconomic evaluation is usually not a precise number, but a range. This is normal, due to the uncertainties in the data and assumptions that must be made in the analysis. As in any good analysis, the assumptions are modified to evaluate the impact on the results. For example, the

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pCODR Final Economic Guidance Report on Venetoclax estimated the value of the ICER as being between $139,074 and $1,474,679\(^7\). What value will be used by the PMPRB?

The CADTH and INESS process deals with this and similar issues by using a committee of experts and providing opportunity for input by stakeholders, notably patient groups and clinicians. Pharmacoeconomic analysis is an input to decision making whose conclusions are tempered by human judgement from both experts and stakeholders.

We do not know how the value of the ICER will be chosen. It was stated during the PMPRB presentation that CADTH “will provide a number”. This turns the price determination process into a black box, because the key input is not knowable and is determined by some unknown process without stakeholder input.

5.1.2 The uncertainty in the determination of the rebates price is a disincentive to the introduction of novel treatments.

We are concerned that it is not only the level of the price that will make manufacturers of innovative medicines avoid Canada, it is the inability to predict or even exert some measure of influence on the price they will be able to charge. Since CADTH and INESS modify the pharmacoeconomic analyses produced by manufacturers and since the conclusion of these analyses are a range of values for the ICER, it is impossible predict the value the PMPRB will use in its calculation of the maximum rebated price.

Why invest a year or two of effort and resources in a process where the outcome is not predictable and there is no possibility of negotiation? This is another reason why we fear that the proposed PMPRB guidelines will discourage pharmaceutical companies from introducing new medicines to the Canadian market.

6 Conclusions

6.1 The negative consequences of the PMPRB proposals will be borne by Canadians, not by the global pharmaceutical companies.

The pharmaceutical industry is a global industry. Drug manufacturers can choose the countries in which they market their products. Faced with an unpredictable and unfavorable regulatory environment, they will shun the Canadian market in favour of better opportunities elsewhere.

The losers will be:

- Canadian patients who will not be able to obtain new innovative therapies. As a result, there will be patients who will die prematurely or suffer a reduced quality of life. They will not have access to alternative therapies should they develop undesirable side effects or if their disease mutates and a new therapy is required.

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\(^7\) pan-Canadian Oncology Drug Review, Final Economic Guidance Report, Venetoclax for Chronic Lymphocytic Leukemia, March 2, 2018
• Canadian medical researchers whose funding from the pharmaceutical industry will be reduced.
• The Canadian taxpayer because time limited treatments with a lower cost over the lifetime of a patient will not be available.

6.2 In principle, the proposed PRPMB 11 is acceptable, providing the introduction of novel treatments and the number of clinical trials is not compromised

We recognize that the high cost of new medicines needs to be addressed. Regulation is required, because the forces that normally control prices in a functioning market are limited by the monopoly power of patentees.

We support the use of external reference pricing because it is a well-known mechanism used in other countries, it is transparent, provides certainty to manufacturers, and has no hidden value judgements.

In summary, we support the implementation of the PMPRB 11, providing the introduction of novel treatments, the number of clinical trials and patient support programs are not compromised.

6.3 The method proposed to set the maximum rebated price must be revised

As explained above, the use of a single value ICER to set a maximum rebated price is unacceptable because of the following:

• The assumptions and value judgement that must be made in a pharmacoeconomic analysis make it impossible to consider a single value ICER as an objective representation of social values.
• The process for determining the value ICER to be used will be determined from the range of values produced by the pharmacoeconomic analysis is unknown.
• The absence of human judgement and stakeholder input in the determination of the maximum rebated price.
• The uncertainty created by the proposed method for setting the maximum rebated price will discourage the introduction of new treatments to Canada.

Sincerely

Raymond Vles
Chair of the Board
CLL Patient Advocacy Group