House of Commons
Standing Committee on Health (HESA)

"Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders"

October 2018

Submission of:

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Introduction

Horizon Therapeutics Canada (Horizon) welcomes the current study **"Barriers to Access Treatment and Drugs for Canadians Affected by Rare Diseases and Disorders"** being undertaken by the House of Commons Standing Committee on Health (HESA).

Horizon is a new innovative pharmaceutical company in Canada focused on developing and commercializing medicines for rare disease and rheumatic disease indications. Horizon aims to improve the lives of Canadians living with rare diseases by bringing innovative therapies to Canada in a safe, timely and sustainable way. Our commitment to our patients – especially in the rare disease space – is grounded in our personal investment in the lives of the people our medicines help, from diagnosis through ongoing care. This study is therefore urgently needed and speaks directly to our corporate mission and daily work.

As you have learned through this study to date, Canadian patients with rare disorders are among the most vulnerable to gaps in access to treatment and care. They need specific attention from our healthcare system and health policy-makers. By definition, each specific rare disease affects only a small number of patients spread across our relatively large country. The level of scientific and clinical knowledge available to diagnose and manage these conditions is fragmented and may vary widely depending on the disease, the local geography, and other unique circumstances. Available treatment options may also be limited: only 60% of globally approved treatments for rare disorders are approved in Canada, and those approvals often come years later than in the United States.[1]

Horizon is a member of Innovative Medicines Canada, BIOTECanada and a forum for other rare disease innovators, which is eager to engage with the Committee on this study. This submission is meant to complement those efforts and respond specifically to some of the issues raised regarding our medicine, PROCYSBI®, indicated for the treatment of nephropathic cystinosis.

PROCYSBI® - for the treatment of nephropathic cystinosis

Our product PROCYSBI (cysteamine bitartrate) remains the first and only Health Canada approved medication for the treatment of nephropathic cystinosis. This is a progressive and, if left untreated, fatal disease. Non-adherence to a cysteamine therapy has been well characterized in the medical literature and is associated with permanent morbidity and life-threatening consequences for patients. PROCYSBI

[1] See Canadian Organization for Rare Disorders, "About Our Work." Available here.

represents a significant advance in treatment that was encouraged by patients and physicians due to the inadequacies of other, unapproved treatment options. The committee has heard evidence of another product, immediate release (IR) Cysteamine, that some Canadian patients were obtaining from the United States under Health Canada's Special Access Programme. To our knowledge, the manufacturer of IR Cysteamine has declined to pursue Canadian market authorization through the normal regulatory channels.

PROCYSBI was the result of a substantial, multi-million dollar clinical research program. Horizon paid for this research when it acquired the company that developed PROCYSBI and has since invested heavily into subsequent extensive work to seek regulatory approval and commercialization of the medicine. The driving motivation for this research program was the established limitations of the existing therapy which had contributed to patient non-compliance and subsequent sub-optimal health outcomes.

Non-compliance due to dosing requirements is an important point of differentiation between PROCYSBI (every 12 hours) and the non-approved alternative treatment, IR Cysteamine (every 6 hours). IR Cysteamine is also associated with substantial side effects that frequently hamper adherence and compliance to therapy. The challenges related to IR Cysteamine have been shown to contribute to suboptimal adherence (as low as 23%) and poor clinical outcomes in patients with cystinosis.[2] Delayed or missed doses contribute to kidney damage and toxicity in other organs. Any accumulation of poor adherence to treatment has been shown to translate to decreased life expectancy. For every year that treatment targets were met, an additional 0.9 years of kidney function was observed. Another previous study in children showed clear benefits in both kidney function and overall physical, social and emotional development with PROCYSBI vs IR Cysteamine.[3]

This clear clinical value of PROCYSBI for Canadian cystinosis patients was affirmed by Health Canada in reviewing Horizon's submission as a Priority Review. Health Canada will only grant Priority Review status in cases of "a serious, life-threatening or severely debilitating disease or condition for which there is substantial evidence of clinical effectiveness that the drug provides:

- effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or
- a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada."[4]

PROCYSBI qualified for Priority Review on both aspects. Having received Health Canada Notice of Compliance (NOC) in June 2017, PROCYSBI has satisfied all requirements for safety, efficacy and product quality – all of which are critically important for patient utilization and outcomes. Horizon is committed to meeting these requirements on an ongoing basis.

Since approval in 2017, Horizon has worked hard to address patient access issues across Canada to ensure that any barriers to treatment were addressed and eliminated. Since approval, PROCYSBI has become the treatment of choice for both new and existing Canadian cystinosis patients. When afforded

[2] Levtchenko EN et al. Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis. *Pediatr Nephrol*. 2006 Jan;21(1):110-3.

[3] Langman CB, Greenbaum LA, Grimm P, et al. Quality of life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate. *J Pediatr*. 2014;165(3):528-33

[4] See Health Canada, *Guidance for Industry - Priority Review of Drug Submissions*, Section 1.4. Available here.

the opportunity for access, a substantial majority of patients and their physicians have transitioned to PROCYSBI.

We are further pleased to advise the Committee that PROCYSBI is now widely reimbursed across Canada by both private and public plans. These milestones were achieved as a function of Horizon working collaboratively on multiple fronts, including with physicians, patients, governments and private payers. Horizon supported patients through a compassionate access program while discussions with the pan-Canadian Pharmaceutical Alliance (pCPA) rapidly progressed. We are proud to say these negotiations were successfully concluded in July of this year. Horizon's work in securing reimbursement for PROCYSBI was also supported by our responsible and fair approach to pricing, with a Canadian list price at the low end of current international markets.

Horizon is hopeful that our ongoing support for patients through the *TranscendRare* support program and our support to a North American cystinosis registry will further ensure that the benefits of PROCYSBI continue to translate into the best possible health outcomes for patients.

Health Canada's Special Access Programme (SAP)

Horizon has noted the Standing Committee's specific interest in the Health Canada Special Access Programme (SAP). Horizon welcomes the recent efforts undertaken by Health Canada to seek broad stakeholder input on issues pertaining to the SAP, including the consultation process which occurred in early 2018. Horizon was pleased to make a submission to Health Canada, and we would be happy to make it available to the Committee at your request. Our perspective on the key policy issues raised is also provided here.

The SAP remains an important regulatory mechanism to facilitate the availability of medically required but unapproved treatments for Canadian patients and their healthcare providers – specifically when patients have no other therapeutic options. It is important to note, however, that in the overall context of challenges for accessing treatments faced by Canadians suffering with rare diseases, the SAP is a relatively minor issue in comparison with the much larger issues pertaining to Canada's overall regulatory, pricing and reimbursement system.

Irrespective of the rationale or specific situations faced by each manufacturer at the international level, it is a continuing business reality of the global biopharmaceutical industry that not all therapies will be submitted or approved in Canada through the normal review channels. With the ongoing and future needs of Canadian patients at the centre of any process, the SAP must sustain a focus on being a predictable and efficient mechanism for all stakeholders while continuing to serve a clear public policy purpose. Moving to a more automated system, for example, would be one way to achieve this objective while enhancing and simplifying the day-to-day functioning of the SAP to the benefit of Canadian patients.

Health Canada has expressed an interest in examining the long-term use of SAP and potential incentives for manufacturers to transition to Canadian market authorization. Horizon believes that this is an important policy discussion which should be approached with careful consideration. In assessing potential reforms, it is fundamentally important to distinguish between those situations where (a) a product has been accessed via SAP and there is minimal to non-existent probability of a forthcoming filing from the

manufacturer, and (b) situations where an SAP product is being transitioned to an approved and marketed product for the same indication.

It would be inappropriate and inadvisable to reduce the regulatory requirements for one manufacturer in circumstances where a competing manufacturer has met the existing submission requirements. The objective should always be to encourage additional submissions to Health Canada according to the established pathways. This should remain the preferred and incentivized route to facilitating access to therapy for Canadian patients, including for rare diseases. SAP cannot and must not be used by manufacturers seeking to achieve Canadian market authorization through a reduced regulatory standard. If manufacturers are able to use SAP to make medicines available in Canada, the entire Health Canada process established to review efficacy, safety and quality for Canadian patients will be undermined.

Communication and consideration of overall regulatory burden is also an important issue to consider in relation to marketed products and unapproved products entering Canada under SAP. As previously noted in this submission, our medicine PROCYSBI (indicated for nephropathic cystinosis) received Health Canada Notice of Compliance in June 2017 following a Priority Review. It is currently the only approved treatment for this indication. Until the approval of PROCYSBI, some Canadian cystinosis patients were accessing a different, unapproved treatment (IR Cysteamine) via the SAP. As the transition due to the approval of PROCYSBI remains ongoing, it is our understanding that Health Canada is only considering new requests for IR Cysteamine in cases where the patient has a medically necessary reason for not taking PROCYSBI as the approved therapy. We believe this is a fair process ensuring that the very small portion of patients who may have a medical reason to continue taking IR Cysteamine continue to have a therapeutic option. Horizon supports patients having a choice among medicines, however it's important that those medicines undergo the established Health Canada process – with the exception of those rare cases where a patient cannot switch to the approved medicine.

Horizon has been diligently focused on ensuring that this transition has been as seamless as possible for patients requiring PROCYSBI, including funding treatment directly in cases where Canadian reimbursement was not in place. However, it is clear from our experience throughout this process that the communications from Health Canada around the SAP operation and rules for the general public could be enhanced and clarified to address any misunderstandings about the SAP. We would strongly encourage both the Standing Committee and Health Canada to underline the value to Canadians of having access to Health Canada approved marketed products and the benefits of moving away from SAP-only availability.

The Importance of Innovation to Treat Rare Diseases

As the Standing Committee is aware, due to the inherent nature of rare diseases, developing and commercializing treatments for these conditions in Canada is more difficult than for more common conditions. Research and product development presents immediate challenges due to increased uncertainty and longer timelines compared to other conditions. Once submitted for approval, rare disease treatments struggle to overcome further barriers within the review and reimbursement processes. This is often exemplified by Canadian public plans covering relatively fewer rare disease treatments, complicating access to treatment for many Canadian patients.

Horizon is actively engaged with our trade associations, including a group of leading rare disease innovators. Consistent with their submission to the Advisory Council on the Implementation of National

Pharmacare, we would highlight below manifold challenges in developing and making available innovative rare disease treatments at each stage of the process in Canada.[5]

Research & Development - Low Prevalence, Uncertainty of Evidence and Limited Expertise

Most biopharmaceutical research implies huge investment risk and ends in failure, and rare disease research is at the riskier end of that spectrum. For many rare diseases, there is often a lack of adequate scientific understanding and relatively few clinical experts. Clinical trial sizes are almost always smaller than average due to the limited number of patients suffering from these conditions, making patient enrollment difficult. This supports the need to recruit patients at the global level across numerous clinical trial sites. Rare disease trials therefore tend to take longer at higher relative costs. In many circumstances, randomized, double-blind studies are often simply not feasible or ethical, leading innovators to rely on alternative research methodologies.

Regulatory

The regulatory environment, pricing and HTA review processes, and reimbursement process make only limited provisions for the exponential challenges that must be overcome to successfully bring a rare disease treatment to market. Key regulatory challenges in Canada include a lack of a dedicated framework with specific tools to incentivize the research and submission of new innovations in Canada. Other leading jurisdictions have also established effective rare-disease specific intellectual property frameworks in recognition of the inherent challenges facing innovators.

Pricing

The pricing of innovative medications is an important area of policy discussion, especially for rare disease treatments due to the context. For any manufacturer to recover up-front investments for these very small patient populations, including all failed research programs (which is often not captured by commentator cost estimates), the eventual price of the resulting innovative medicines will inevitably be much higher than more common treatments on a per-patient basis. But it is critically important to note that the overall budget impact for rare disease therapies is low in the context of total spending on medications, and even smaller in the context of healthcare overall. Rare disease spending is effectively a fraction of a fraction within Canada's $242 billion total health expenditure.[6] Using PROCYSBI as an example, there are less than 100 people living with cystinosis in Canada. The strain on the health budget is miniscule, yet the medicine provides tremendous benefit to an isolated community managing the daily struggles of a devastating disease.

Under Canada's current system of price regulation through the Patented Medicine Prices Review Board (PMPRB), it is often challenging for a rare disease treatment to pass the PMPRB's tests for excessive pricing. Proposed reforms to the PMPRB's regulations and guidelines will only exacerbate this issue. Of significant concern is the proposal to apply health economic factors to price regulation that is deeply flawed.[7]

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[5] See submission to the Advisory Council on the Implementation of National Pharmacare from Canadian Rare Disease Innovators, available here.

[6] Canadian Institute for Health Information (2017 forecast).

[7] See Law and Critchley, Ottawa's plan to change drug price regulations is not good policy, *Policy Options,* October 12, 2018.

The proposed PMPRB reforms would move the mandated price threshold to a level that rare disease treatments realistically cannot meet. Overall, it will be even more difficult for the price of a rare disease medicine to be deemed "non-excessive." The bottom line on price regulation is that any policy change which results in it being more uneconomical for an innovator to pursue market access in Canada risks the viability of current and future treatments being available for the Canadian patients who need them.

Reimbursement

Regulatory and pricing compliance are not sufficient to ensure Canadians have access to the innovative treatments they may require, especially for rare diseases. Mandatory for public reimbursement, Health Technology Assessment (HTA) processes are challenged to account for the small clinical trial sizes and resulting evidence packages associated with innovative rare disease treatments. These innovations also often struggle to meet inappropriate cost/benefit thresholds that have been established for medications designed for larger disease populations. There is also a lack of practical therapeutic perspective applied in these reviews. Collectively, these factors have resulted in very low recommendation rates for innovative rare disease therapies at the national level in Canada from the Canadian Agency for Drugs and Technologies in Health (CADTH). [8]

Even when CADTH positively recommends a rare disease treatment, there are still major challenges to public reimbursement. Many positive recommendations may come with specific direction to seek lower prices, which may or may not jeopardize the feasibility of marketing a medicine. The pan-Canadian Pharmaceutical Alliance (pCPA) then negotiates additional price reductions with manufacturers jointly on behalf of all the Canadian public drug programs. However, the pCPA lacks a dedicated pathway for rare disease treatments, and negotiations typically take much longer than for other innovative medicines. Even after a successful joint negotiation, a given public plan will not necessarily add the medicine to its formulary in a predictable fashion, a process may extend over many months and sometimes years. This variation in timing remains a barrier for conducting good faith negotiations in Canada in the interests of patient access to innovative therapies.

Although some provincial / territorial drug plans have created processes for reimbursement of certain rare disease treatments, these are extremely specific to a very limited number of these treatments. In most jurisdictions, and for most rare disease treatments, no special provisions are made to ensure patients can access these medications.

The Standing Committee has received some evidence from witnesses with respect to appropriate cost thresholds and its relation to fairness in making health expenditure decisions. These are complex and important discussions. In the context of rare disease treatments, Horizon would encourage a more nuanced perspective which holds that all Canadians deserve a fair opportunity at achieving a meaningful health gain, which includes patients with rare diseases. Many rare diseases have specific characteristics which merit much closer policy attention, including severity, prevalence in children and youth, and lack of other effective treatment options. This perspective has supported different and unique funding approaches for rare diseases in other international jurisdictions. We would encourage Canada to explore the most appropriate reimbursement models, including the potential application of "National

[8] Menon D et al. Reimbursement of Drugs for Rare Diseases through the Public Healthcare System in Canada. Where Are We Now? *Healthcare Policy*. 11(1) August 2015. 15-32.

Pharmacare," to help address the unique needs of Canadian rare disease patients and the health plans tasked with funding their treatment.

Rare disease innovators including Horizon are open to working with payers and public agencies to explore innovative ways to reimburse rare disease treatments. This includes exploring managed entry agreements and conditional approvals to help payers manage budgets while improving timely access to treatment. Now, with a national conversation underway to create pan-Canadian public coverage for medications, we have a shared opportunity to make improvements to the overall system. By recognizing the unique needs of rare disease treatments, Canada can accelerate innovation in this country while alleviating the suffering of many thousands of Canadians with life-threatening or life-altering conditions.

Recommendations for the Standing Committee on Health

1. Canadian market authorization is and should remain the preferred regulatory pathway for pharmaceuticals, including treatments for rare diseases. This ensures Health Canada's rigorous assessment of acceptable benefit/risk and scientific evidence, medicine quality, and labelling requirements are met. Each of these aspects have been put in place for well-defined public policy purposes.

2. Companies which have made the necessary investments and taken the required steps to fulfill Health Canada's requirements for market authorization should never be disadvantaged or dis-incentivized due to any other efforts, however well-intentioned, to incentivize a different manufacturer of a competing product available under SAP to submit for market authorization. The regulatory "bar" should be consistent and not be lowered – which would do a disservice to the integrity of the regulatory process and patient safety, as well as sending the wrong message to innovators pursuing risky and expensive clinical programs to advance new therapies.

3. The SAP can be reformed while retaining its core function and retaining the integrity of the overall Health Canada review process. Moving to a more automated system, for example, would be one way to achieve the objective of increased efficiency while enhancing and simplifying the day-to-day functioning of the SAP to the benefit of Canadian patients.

4. Because developing and commercializing treatments for rare diseases in Canada is unique and difficult, special consideration at the policy level is warranted to address development, regulatory, pricing and reimbursement issues. Horizon is supportive of Canada pursuing a dedicated rare disease policy framework to ensure that Canada remains at the forefront of incentivizing the development, registration, and availability of these important innovations for Canadian patients.

5. The current National Pharmacare conversation in Canada represents an exciting opportunity to advance an integrated and sustainable policy framework to ensure that Canadians with rare diseases have timely, equitable, appropriate and sustainable access to the highest quality of care available. Horizon would respectfully urge the Standing Committee to send a strong message that Canadians suffering from rare diseases should not be left behind in any Pharmacare policy plan.