PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the *Patent Act*
R.S.C. 1985, c. P-4, as amended

AND IN THE MATTER OF
Horizon Pharma (the "Respondent")
and the medicine Cysteamine Bitartrate sold by the Respondent under the trade name PROCYSBI®

RESPONSE
of Horizon Pharma
(dated February 18, 2019)

Overview

1. The Respondent, Horizon Pharma ("Horizon"), opposes this Application for an Order pursuant to sections 83 and 85 of the *Patent Act* (the "*Act*") that Horizon is selling, or has sold, the medicine PROCYSBI® in any market in Canada at a price that is, or was, excessive.

2. Horizon asks for an Order dismissing this Application on the grounds that:

   (a) the price at which Horizon is selling, or has sold, PROCYSBI® is non-excessive;

   (b) the patented medicine PROCYSBI®:

      (i) is an orphan disease medicine that has revolutionized the treatment of patients suffering from nephropathic cystinosis;

      (ii) is a breakthrough, or in the alternative, a substantial improvement, or in the further alternative, at a minimum, a moderate improvement, because patients who may now benefit from the patented invention embodied in PROCYSBI®:

(A) may live out to their adult years;

(B) may delay the progress of renal failure associated with cystinosis;

(C) may experience a significant reduction in side effects, including significant GI-related adverse events and halitosis, that improves compliance leading to increased efficacy;

(D) will reduce the dosing schedule (from four times daily to two times daily) and will improve compliance, enhance quality of life and convenience, enable adequate periods of sleep, and therefore increase efficacy;

(iii) was granted Priority Review Status by Health Canada on December 24, 2015, "on the basis of the indication being for a life-threatening rare lysosomal storage disease typically diagnosed in early childhood for which there is currently no drug approved in Canada," a decision made in accordance with Health Canada's policy on Priority Reviews, which are reserved for drug submissions related to the treatment and prevention of serious, life-threatening or severely debilitating illnesses or conditions where there is no existing drug product on the Canadian market with the same profile or where the new product represents a significant improvement over existing therapies;

(iv) is the first drug product to receive, a notice of compliance in Canada from Health Canada with respect to cystinosis, recognizing:

(A) the safety, quality, and effectiveness of PROCYSBI® in the treatment of cystinosis;

(B) that PROCYSBI® is the first drug product to be sold in Canada that effectively addresses the treatment of cystinosis;

(v) is listed on Health Canada's register of innovative drugs;

(vi) is the subject of the inventions disclosed and claimed in Canadian Patent Nos. 2,640,531 ("531 Patent") and 2,914,770 ("770 Patent"), granted by the Canadian Intellectual Property Office, which do not relate to cysteamine bitartrate *per se* but instead to the inventions described below that have been life-changing for patients and which are embodied in PROCYSBI®;

(vii) is provided to all patients who are prescribed PROCYSBI®, regardless of their insurance coverage or ability to pay. Horizon ensures that no patient in Canada has to pay out of pocket for PROCYSBI®, as each patient is fully covered through private insurance, provincial and federal drug plans, and supported by Horizon's patient support program that covers co-payments and provides free PROCYSBI® to patients with no drug plan coverage;

(viii) is the subject of listing agreements through which public payers have secured the availability of this much sought-after and necessary patented medicine for those few patients suffering from this rare disease, at reasonable, negotiated prices:

(A) at a per unit, net price which is among the lowest international prices;

(B) with a per patient annual expenditure cap; and

(C) with a per jurisdiction annual budget cap;

which listing agreements cover all known Canadian patients with nephropathic cystinosis;

(ix) is currently offered at a list price in Canada that:

(A) is reasonable in terms of an introductory price, which is non-excessive in view of the Board's Guidelines;

(B) is below the median international list price of PROCYSBI®; and

(C) is one of the lowest list prices in the world for PROCYSBI®;

(c) Horizon has been denied procedural fairness and transparency, because of the following conduct of Board Staff:

(i) refusing to apply its own Guidelines and long-standing past practices in determining whether the price of PROCYSBI® was non-excessive, and using undisclosed *ad-hoc* rules and data to determine that the price of PROCYSBI® was excessive;

(ii) relying on a report from the Canadian Agency for Drugs and Technologies in Health ("CADTH"), when those members:

(A) disregarded evidence that PROCYSBI® will lead to improved compliance and efficacy because of the differences between this patented medicine and cysteamine bitartrate;

(B) ignored the serious adverse health consequences that even short periods of non-compliance present for cystinosis patients; and

(C) relied on a report of the Canadian Drug Expert Committee (CDEC), which concluded, to the prejudice of cystinosis patients, that "[w]hile delayed-release cysteamine may increase life expectancy compared with no treatment, it is also associated with a high rate of complications **since patients live longer, which increases the total health care costs"** [**emphasis added**];

(iii) relying on the erroneous recommendation of the Human Drug Advisory Panel ("HDAP"), both in terms of its classification of the therapeutic effect of PROCYSBI® and its identification of therapeutic class comparators, when:

(A) two of its members were members of the above-noted CADTH Review; and

(B) Board Staff improperly influenced HDAP by requiring HDAP to consider Cystagon as a comparator.

Horizon Pharma

3. Horizon is a biopharmaceutical company focused on researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. By fostering a growing pipeline of medicines in development and exploring all potential uses for currently marketed medicines, Horizon strives to make a powerful difference for patients, their caregivers and physicians. Founded in 2008 as a startup with only a handful of employees and no office space, Horizon now has over 1,000 employees worldwide and eleven medicines, the majority, like PROCYSBI®, treating rare diseases. Horizon has a growing team in Canada committed to bringing forward innovative new rare disease medicines. In addition to PROCYSBI®, Horizon makes two other medicines available in Canada for very rare diseases.

4. ***Orphan drugs.*** Orphan drugs are drugs that treat rare diseases. However, orphan drugs are not less expensive to develop than medicines that treat larger patient groups. Smaller patient populations inherently mean more expensive prices to bring these medicines to the market, as there are profoundly fewer sales over which to recoup expenses and earn a reasonable return. The regulatory expenses and associated costs imposed on Horizon to bring a drug to market do not materially decrease for orphan drugs. Historically, these realities left research and development focused on these vulnerable patient populations unfunded or underfunded.

5. Recognizing the challenges of bringing orphan drugs to the patients that need them, the United States Food and Drug Administration ("FDA") maintains an Office of Orphan Products Development ("OOPD"). The mission of the OOPD is to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis or treatment of rare diseases or conditions. The OOPD provides incentives for sponsors to develop products for rare diseases. The OOPD program has successfully enabled the development and marketing of over 600 drugs and biologic products for rare diseases since 1983. In contrast, fewer than ten such products supported by industry came to market between 1973 and 1983.

6. Yet, no such orphan drug incentivization system exists in Canada, other than the incentives offered by the patent system and the *Act*. Consequently, only a fraction of orphan drugs approved by the FDA in the United States are also approved by Health Canada under a notice of compliance in Canada.

7. ***PROCYSBI®.*** Horizon is the manufacturer of PROCYSBI®, a patented medicine containing a delayed release formulation of enterically-coated, microspherized beads of cysteamine bitartrate indicated for the treatment of nephropathic cystinosis (as explained in more detail below). PROCYSBI® is sold in Canada in 25mg and 75mg oral capsules.

Nephropathic Cystinosis

8. Cystinosis is a rare lysosomal storage disorder in which lysosomal membrane transport of cystine is impaired in cells throughout the body. Cystinosis is characterized by toxic levels of cystine that accumulate within the lysosomes, eventually causing cystine crystals to form. The cystine crystals damage cells and target organs, leading to functional pathology. Without specific treatment, patients (most often children) with cystinosis develop end-stage kidney failure at approximately age nine. Other complications include shortened lifespan, failure to thrive, diabetes, dehydration, corneal opacity, delayed puberty, hypothyroidism, renal tubular dysfunction, nephropathy, and nephrogenic diabetes insipidus.

9. Supportive treatments and multiple healthcare disciplines – including specialists such as pediatric nephrologists and surgeons – are required to manage the multi-organ impact of cystinosis. The incidence of end-stage renal disease in a study of patients with cystinosis was 91% with the median age at diagnosis of 9.9 years old. Kidney transplant is the result of end stage renal failure. In a study with patients with untreated cystinosis, 92% required a kidney transplant by age ten. Enormous sums are required to effectively treat these medical complications over the entirety of a cystinosis patient's lifetime. Even after transplant surgery, the disease must be treated, as kidney transplantation does not correct the underlying metabolic defect in other tissues.

10. Nephropathic or "classic infantile" cystinosis – the most common and most severe form of the disease – is typically diagnosed in infancy and requires lifelong cystine depleting therapy. Progressive renal impairment at an early age is the foremost clinical manifestation of cystinosis. If left untreated, cystinosis leads to significant morbidity and premature death. In patients with cystinosis, all organs are impacted as time progresses, and without treatment, elevated levels of cystine can lead to irreversible organ damage.

11. Cystinosis is extremely rare. Cystinosis is estimated to occur in about one out of every 100,000 to 200,000 births. Approximately 2,000 people worldwide are currently diagnosed with nephropathic cystinosis. In Canada, roughly 100 Canadians have cystinosis at any one time (with a higher incidence of cystinosis observed in Quebec); in the United States, the number is between 500 and 600.

The Treatment of Cystinosis with Cystagon

12. Cysteamine, the active pharmaceutical ingredient ("API") in both Cystagon and PROCYSBI®, has been used to treat cystinosis since as early as 1974. Cysteamine lowers cystine levels, delaying or preventing the complications of cystinosis. Treatment with cysteamine significantly decreases and delays the incidence of end-stage renal disease, diabetes, and neuromuscular disorders, and overall survival. Each year of effective cystine control preserves nearly one year of kidney function. Every year that patients maintain mean leukocyte cystine levels below the target level of <1 nmol ½ cystine/mg protein results in 0.9 years of kidney preservation. Cystine control is therefore essential for patients with cystinosis. But maintaining cystine levels below this critical level is difficult – cystine levels rise rapidly in the absence of an effective does of cysteamine.

13. Cystagon is a capsule form of immediate-release cysteamine bitartrate, manufactured by Mylan Pharmaceuticals Inc. ("Mylan"). Cystagon received regulatory approval in the United States on August 15, 1994, and in Europe on June 23, 1997. Before the 1990s, liquid forms of the drug might have been available. But neither Mylan, nor any other manufacturer, has ever sought approval to market Cystagon in Canada. Cystagon is not an approved drug product in Canada. It does not have a notice of compliance in Canada. Cystagon is neither listed on Health Canada's notice of compliance database nor does it have a drug identification number (DIN)

issued by Health Canada. Instead, Mylan has made Cystagon available to Canadian patients, as an unapproved drug, through the Special Access Program (SAP) since 2000. Cystagon is not a patented medicine.

14. Immediate-release cysteamine (*i.e.*, Cystagon) has poor adherence, or patient compliance. Cystagon must be taken every six hours, without fail, which results in lack of sleep and scheduling difficulties. The drug is also associated with tolerability issues, gastrointestinal issues, and demoralizing social stigma issues, such as sulfuric body and breath odour. Immediate-release cysteamine's taste and smell are also offensive to many patients: it has the taste and smell of rotten eggs, which can lead to nausea and vomiting. Additionally, metabolites of cysteamine, dimethylsulfide and methanethiol are excreted in breath and sweat, resulting in significant halitosis and body odour. This often leads to children experiencing social isolation and bullying.

15. Patients and their caregivers can never receive an uninterrupted night's sleep if they adhere to the six hour dosing schedule. Medication must be carried for most activities and administered at school for younger patients, often by a feeding or gastronomy tube ("G-tube"), adding to the stigma of the disease.

16. Cysteamine is a notoriously potent gastric acid stimulant (it is often used to induce ulcers in laboratory animals). Non-enteric-coated immediate-release cysteamine (*i.e.*, Cystagon) often results in rapid initial gastric secretion, leading to serious gastrointestinal issues.

17. Roughly half of the children who need to take cysteamine cannot swallow capsules. In those cases, parents have to open up a capsule, mix the contents with water, and put the mixture in a G-tube. Not only is this administration tedious (leading to further sleep deprivation of caregiver and patient), it also reduces the effectiveness of the drug.

18. These flaws with immediate-release cysteamine lead to extremely high rates of noncompliance. Studies have suggested that as few as 23% of patients are compliant with the six hour dosing schedule. And the consequences are severe. Brief interruptions in cysteamine dosing results in the accumulation of cystine to toxic levels during the day or night. Delaying treatment by as little as three hours can result in cystine levels rising by up to 40%.

19. This non-compliance has significant implications for life expectancy. Strict adherence is key to delaying or preventing cystinosis complications: more time on cysteamine therapy at precise intervals means preserved kidney function and a lower incidence of diabetes, lower incidence of pulmonary dysfunction and longer survival. Studies suggest that adherence to immediate-release cysteamine is increasingly challenging as patients age. The halitosis and body odour resulting from cysteamine administration can make it difficult to convince adolescents to take the drug.

20. Because of the poor compliance associated with immediate-release cysteamine, the life expectancy and prognosis of patients being treated with immediate-release cysteamine is poor.

21. Additionally, because Cystagon does not have marketing authorization in Canada, no Canadian product monograph exists, no instructions for use for Canadian patients, no Health Canada approved packaging and labelling, no safety, quality, and efficacy data on file at Health Canada for Cystagon in Canada.

22. As is explained in detail below, PROCYSBI® was developed to solve the serious efficacy, side effects, and compliance issues experienced with immediate-release cysteamine. The patented medicine PROCYSBI® resulted because of the long unmet need, in this tiny patient population, realized by physicians treating these patients.

The development of PROCYSBI®

23. Jerry Schneider, a pioneering pediatric clinician in the treatment of cystinosis at the University of California – San Diego ("UCSD"), is one of the named inventors on the 531 Patent. Ranjan Dohil, a pediatric gastroenterologist at UCSD, is the other named inventor on the 531 Patent.

24. In the 1999-2000 timeframe, Dr. Schneider approached Dr. Dohil for technical assistance. Dr. Schneider had been studying cystinosis in a group of patients and was concerned about significant issues that his patients were encountering with cysteamine treatment. These patients were facing a life-long treatment regimen of having to take cysteamine every six hours.

25. As noted above, cysteamine is ulcerogenic. Immediate-release capsules are often absorbed in the stomach, causing rapid absorption and significant gastrointestinal ("GI") difficulties. In the course of acid-secretion studies they performed, Dohil and Schneider detected that administration of cysteamine to the small intestine rather than the stomach resulted in a significant, unexpected increase in the amount of cysteamine absorbed.

26. Dr. Dohil and Dr. Schneider engaged in extensive studies, scientific research and clinical evaluations with the hope, and ultimate success, of reducing the dosing schedule necessary to effectively control cystine levels and mitigating the worse of the adverse side effects associated with immediate-release cysteamine.

27. After obtaining an exclusive license to UCSD technology, Raptor Pharmaceuticals (later acquired by Horizon) took on the significant costs and risks to advance the clinical development program that led to the FDA approval of PROCYSBI®. More than US$180 million was invested to conduct clinical trials evaluating the safety and efficacy of PROCYSBI®, secure regulatory approvals, and perform ongoing post-marketing research.

28. PROCYSBI® has been approved in the United States since 2013 and in Canada since 2017. Although it is a new drug used to treat a rare disease, the evidence and real-world observations are that PROCYSBI® is a profoundly better drug, offering significantly better clinical outcomes and, as Health Canada recognized, is effectively the first real treatment of cystinosis in Canada.

The PROCYSBI® Patents and the Patented Medicine

29. ***The PROCYSBI® Patents.*** Horizon is a licensee of Canadian Patent No. 2,640,531 (entitled "Enterically Coated Cysteamine, Cysteamine and Derivatives Thereof" and issued January 3, 2017) (the "531 Patent"), which is licensed to Horizon by the Regents of the University of California. Horizon owns the other patent relevant to this proceeding, Canadian Patent No. 2,914,770 (entitled "Delayed Release Cysteamine Bead Formulation, and Methods of Making and Using Same" and issued September 27, 2016). As described in more detail below, both patents relate to particular formulations utilized in the making of PROCYSBI®.

30. The 531 Patent is entitled "Enterically Coated Cysteamine, Cystamine and Derivatives Thereof". It describes enterically coated cystamine or a cystamine derivative, including a coated cystinosis therapeutic agent that has increased uptake in the small intestine compared to a non-coated cystinosis therapeutic agent when administered orally.

31. The 770 Patent is entitled "Delayed Release Cysteamine Bead Formulation, and Methods of Making Same." It describes delayed release formulations of cysteamine, including an enterically-coated cysteamine composition to facilitate delivery of cysteamine to the small intestine and resulting in less frequent dosing compared to non-enteric coated cysteamine.

32. Cysteamine bitartrate is not the invention of the 531 and 770 Patents (the "PROCYSBI® Patents"). As noted, cysteamine bitartrate has been available, in the United States, since at least 1994. Liquid forms of cysteamine were available earlier. Cysteamine bitartrate is neither a patented medicine nor is cysteamine bitartrate in the class of patented medicines at issue here. Rather, the inventions in the PROCYSBI® Patents are directed to enterically-coated, microspherized beads of cysteamine bitartrate in order to deliver the drug to the small intestine.

The Benefits of PROCYSBI®

33. For the first time, PROCYSBI® allows cystinosis patients to follow a twelve hour dosing schedule, rather than the six hour dosing schedule required for Cystagon. PROCYSBI® is associated with at least the following key benefits:

(a) ***Improved efficacy through better absorption:*** PROCYSBI® is delivered to a different site for absorption (the small intestine) and has a different pharmacokinetic profile that results in increased efficacy and a reduction in the incidence or grade of important adverse reactions. Further, the mean daily dose of PROCYSBI® needed to maintain comparable white blood cell cysteine levels is lower than the mean daily dose of Cystagon.

(b) ***Improved efficacy through better compliance:*** The twelve hour dosing schedule of PROCYSBI® lessens patient and caregiver burden, which reduces sleep disruption, promotes better adherence, and therefore improves efficacy.

(c) ***Reduced side effects:*** Improved GI tolerability, reduced frequency and severity of halitosis and body odour with PROCYSBI® improves adherence and compliance to cysteamine therapy and that translates into more effective control of cystinosis and improved patient outcomes. Treatment with PROCYSBI® is associated with an 87% reduction in the use of concomitant proton pump inhibitors compared with treatment with immediate-release Cysteamine.

(d) ***Improved route of administration:*** Bioequivalence studies have additionally demonstrated that PROCYSBI® sprinkled on a small amount of food or liquid (apple sauce and/or orange juice) is bioequivalent to PROCYSBI® taken as a whole capsule. This is important as it allows patients with swallowing problems to take the therapy in another manner without affecting the stability or bioavailability of the drug.

The commercialization of PROCYSBI®

34. In order to commercialize PROCYSBI®, Horizon and its predecessors engaged in extensive research and development, including the initiation and completion of nine clinical trials. The total investment required to bring PROCYSBI® to market is in excess of US$180 million. To obtain marketing authorization (*i.e.*, a notice of compliance) for PROCYSBI® in Canada, Horizon filed with Health Canada the safety and efficacy data required to support a new drug submission, including substantial information on pre-clinical and clinical trials.

35. Horizon filed its new drug submission (NDS) on January 21, 2016 (filed in the name of the predecessor-in-title to Horizon, Raptor Pharmaceuticals Inc.) and received its notice of compliance from Health Canada on June 13, 2017.

36. On December 24, 2015, Health Canada granted Priority Review to the forthcoming submission for PROCYSBI®. Health Canada maintains a Priority Review policy to ensure that the review of potentially life-saving drugs are fast-tracked and reviewed as quickly as possible. Priority Review is within the discretion of Health Canada, but may be available for drug submissions related to the treatment and prevention of serious, life-threatening or severely debilitating illnesses or conditions:

(a) where there is no existing drug product on the Canadian market with the same profile; or

(b) where the new product represents a significant improvement over existing therapies.

37. Health Canada granted Priority Review for PROCYSBI® "on the basis of the indication being for a life-threatening rare lysosomal storage disease typically diagnosed in early childhood for which there is currently no drug approved in Canada."

38. Horizon made its first sale of PROCYSBI® 25 mg and 75 mg delayed-release capsules in Canada on September 7, 2017.

The Pricing of PROCYSBI®

39. At the date of first sale of PROCYSBI® 25 mg and 75 mg delayed-release capsules in Canada on September 7, 2017, the introductory price was set below the Median International Price, namely, $10.35 for each 25 mg delayed release capsule and $31.05 for each 75 mg delayed release capsule.

PROCYSBI®'s Pricing is Non-Excessive

40. PROCYSBI®'s introductory price is non-excessive, having regard to a number of factors, explained in greater detail below:

(a) the factors set forth in section 85 of the *Act* and PMPRB's Guidelines, which demonstrate that PROCYSBI® is a breakthrough medicine, or at the very least a substantial improvement over Cystagon;

(b) pricing in other jurisdictions;

(c) formulary listing agreements with the provinces, territories, and various federal programs;

(d) the non-excessive return on investment for Horizon; and

(e) Horizon's commitment to ensuring that all patients who are prescribed PROCYSBI® can access it, regardless of their ability to pay.

Horizon's introductory price for* PROCYSBI® *is grounded in the Guidelines

41. The determination of whether the price of a patented medicine is excessive must be made in accordance with sections 79, 83 and 85 of the *Act*. The implementation of the Guidelines and their application must be consistent with the *Act*, as this Board has consistently ruled. Further, the Board has noted that the Guidelines provide fair, practical and predictable results.

42. ***PROCYSBI® is a breakthrough drug.*** Under the Guidelines, a medicine is a "breakthrough drug" when it is the first drug sold in Canada that *effectively* treats a particular illness or indication. HDAP and the Board Staff have improperly excised the word "effectively" from the regulatory language to deny PROCYSBI® the breakthrough designation.

43. PROCYSBI® is the first patented medicine sold in Canada that effectively treats nephropathic cystinosis. For the first time, cystinosis patients – in the real world – can consistently comply with the necessary dosing schedule to control their cystine levels within a normal range and largely avoid the adverse effects of immediate-release cysteamine that historically have caused exceptionally high non-compliance rates. With cystinosis, effective compliance is the only effective treatment.

44. Contrary to Board Staff's allegations, there is no other drug that is a comparator for PROCYSBI®. PROCYSBI® is therefore a breakthrough. Cystagon is not the same medicine as PROCYSBI®, nor is Cystagon in the same therapeutic class as PROCYSBI®. The medicine for the purposes of the *Act* is that to which the invention pertains – namely the patented medicine: enterically coated, microspherized beads of cysteamine bitartrate. Cystagon is not in the class of patented medicines to which PROCYSBI® belongs – the class of patented medicines comprises delayed-release enterically coated, microspherized beads of cysteamine bitartrate. Indeed, PROCYSBI® is the only medicine utilizing the patented inventions.

45. PROCYSBI® is properly categorized as a breakthrough drug, as Cystagon was never approved or sold in Canada and was only available through Health Canada's SAP. PROCYSBI® is the first drug of its kind that is approved to treat nephropathic cystinosis in Canada.

46. In using Cystagon as a comparator, and insisting to HDAP that it had to consider Cystagon as a comparator, Board Staff has departed, for the first time, from its practice of not

utilizing as comparators drugs that have no publically available price. Horizon states that it is not aware of any other instance where Board Staff has departed from its long-standing practice and has used, as a comparator, a drug that has no publically available price.

47. It is in appropriate to use as a comparator a non-patented, unapproved drug, like Cystagon, because it is not the subject of any pricing constraints of payers or the PMPRB and has no public price. The pricing of such non-patented, unapproved drugs is uncertain, is not transparent, is not public and can be inconsistent. Board Staff's recent practice in reviewing the pricing of orphan drugs has been to disregard the pricing of non-patented, unapproved drugs as comparators and to default to the international price of the orphan drugs.

48. Under the Guidelines, a breakthrough drug is not excessively priced if its Canadian price does not exceed the Median International Price. At the date of its first sale, PROCYSBI®'s introductory Canadian price was set below the Median International Price and was therefore non-excessive.

49. ***In any event, PROCYSBI® is a substantial improvement.*** Alternatively, to the extent that Cystagon is in the same therapeutic class as PROCYSBI®, PROCYSBI® is a substantial improvement over Cystagon by virtue of the patented medicine in PROCYSBI®, namely enterically coated, microspherized core beads of cysteamine bitartrate, the subject of the PROCYSBI® Patents. The use of this patented medicine delivers a substantial improvement over Cystagon.

50. PROCYSBI® is a substantial improvement having regard to the primary factors identified by the Guidelines:

(a) ***Increased efficacy:*** PROCYSBI® is delivered to a different site for absorption (the small intestine) and has a different pharmacokinetic profile that results in increased efficacy. Further, the mean daily dose of PROCYSBI® needed to maintain comparable white blood cell cysteine levels is lower than the mean daily dose of Cystagon. PROCSYBI® has increased efficacy for patients suffering from cystinosis because patients are more compliant in taking a patented medicine that is dosed every twelve hours compared to a medicine that is dosed every six hours.

Real world evidence demonstrates that better compliance results in increased efficacy and can lead to extended life spans.

(b) ***Reduced incidence or grade of importance adverse reactions:*** Further, as set out above at paragraph 33, PROCYSBI® results in a significant reduction of the incidence and grade of important adverse reactions, including halitosis and GI complications.

51. The Guidelines provide that factors such as mechanism of action, whether the drug is a new chemical entity and whether the new drug has a different pharmacokinetic profile are not to be taken into consideration, unless the impact of these factors results in increased efficacy and/or a reduction in the incidence or grade of important adverse reactions, as is the case of PROCYSBI® in comparison with Cystagon. Thus, the allegations in the Statement of Allegations that PROCYSBI® and Cystagon have the same mechanism of action and have the same active ingredient are irrelevant to assessing the level of therapeutic improvement of PROCYSBI®. These allegations disregard the increased efficacy and reduction in the incidence or grade of important adverse reactions brought about by PROCSYBI® therapy pursuant to the patented features of the inventions.

52. Under the Guidelines, a substantial improvement drug is not excessively priced if its Canadian price does not exceed the Median International Price. At the date of its first sale, PROCYSBI®'s introductory Canadian price was set below the Median International Price and was, thus, non-excessive.

53. ***If PROCYSBI® is a moderate improvement, the Median International Price is the non-excessive price.*** Horizon maintains that PROCYSBI® is a breakthrough or substantial improvement. However, in the further alternative, even if the Board determines it is a moderate improvement, the non-excessive price for PROCYSBI® is the Median International Price. As set out above at paragraphs 44-47, there is no comparator for PROCYSBI® sold in Canada.

54. The Board's Guidelines are clear that the comparators for a new patented drug product will be those existing drug products, with the same chemical entity, that are *available*, unless the patentee claims and HDAP identifies therapeutic improvement.

55. Cystagon cannot form part of the therapeutic comparator class because:

(a) PROCYSBI® has been identified as having therapeutic improvement over Cystagon;

(b) an SAP drug like Cystagon has no publicly available price;

(c) a non-patented drug like Cystagon is not the subject of any pricing constraints with payers or PMPRB, so its pricing is uncertain, is not transparent, is not public and can be inconsistent;

(d) Cystagon does not appear in any of the six "sources" listed in the Guidelines; and

(e) Cystagon does not have a notice of compliance or drug identification number.

56. In particular, while Board Staff have based the price of Cystagon off of an obscure internet listing of the Newfoundland and Labrador Department of Health and Welfare purportedly published on October 25, 2017, Horizon disputes this price, and puts Board Staff to the proof thereof, because:

(a) Horizon could not independently locate that reference;

(b) to the extent that the internet reference was published, which is denied, it was published in October 2017 alone: no monthly formulary since that time lists Cystagon, nor has any monthly formulary prior to that time listed Cystagon;

(c) the province of Newfoundland and Labrador has no cystinosis patients; and

(d) the province of Newfoundland and Labrador has never listed Cystagon on its formulary.

57. To assign PROCYSBI® either a mid-point between therapeutic class comparison (where there is no comparator and no public price for a comparator) and the Median International Price or a 75% reduction in price, as proposed by Board Staff, would depart from past practice established by Board Staff and from the Guidelines and would not be an appropriate benchmark in setting the maximum non-excessive price in this case.

Proposed pricing is equal to other jurisdictions and provides a non-excessive return

58. Horizon's proposed price in Canada is one of the lowest prices in the world compared to other jurisdictions where PROCYSBI® is available, and provides a non-excessive return over the life of exclusivity.

Provinces have successfully agreed to a discounted price for PROCYSBI®

59. Mandatory price negotiation is carried out by all jurisdictions under the pan Canadian Pharmaceutical Alliance (pCPA). This step in the reimbursement process is intended to reduce the price of drugs whose therapeutic value has been recognized, but whose cost appears to exceed payers' perceived means. Since the inception of the pCPA, drug prices have been brought down significantly. This mechanism is specifically adapted to each drug considered for reimbursement, and it effectively reaches an appropriate balance between patient access to new, life-altering therapies and affordability.

Pricing has not limited patient access

60. Horizon provides PROCYSBI® to all patients to whom it is prescribed, regardless of their insurance coverage or ability to pay. Horizon has ensured that Canadian patients that are not fully covered through private insurance, provincial, territorial, and federal drug plans are covered by Horizon's patient support program that covers co-payments and provides free PROCYSBI® to patients with no drug plan coverage. No concern exists that PROCYSBI®'s price limits access to those Canadians who need it.

The Board's Decision Should Account for the Future of Orphan Drugs like PROCYSBI®

61. Far from requiring a departure from the Guidelines, Horizon submits that policy imperatives require that the Board follow the approach set out in the Guidelines, and determine that PROCYSBI®'s price is non-excessive. Any determination to the contrary threatens the viability of orphan drugs in the Canadian market, to the detriment of Canadians who benefit from these therapies.

62. ***Horizon's investment in PROCYSBI® and the Canadian market.*** In excess of US$180 million was invested to create PROCYSBI®. This fact reinforces that medicines treating rare

diseases/small patient populations are not meaningfully cheaper to develop than medicines that treat larger patient groups. The regulatory costs imposed on marketing a drug in Canada – including demonstrating safety, quality, and efficacy to Health Canada – do not materially decrease for orphan drugs. Smaller patient populations inherently mean more expensive prices to bring these medicines to the market, as there are profoundly fewer sales over which to recoup expenses and earn a return.

63. ***International and Canadian approaches to orphan drugs.*** The FDA has recognized the difficulty in bringing an orphan drug to market through the OOPD, which provides incentives for sponsors to develop products for rare diseases. No such orphan drug incentivization system exists in Canada, aside from the incentives set out in the *Act*; as a result, only a fraction of orphan drugs that have marketing authorization from the FDA in the United States also have marketing authorization from Health Canada.

64. The purpose of the *Act* is to promote and encourage innovation by offering a time-limited period of exclusivity in which the patentee may seek to recover a justified return on its investment, made for the purpose of disclosing its invention to the public and commercializing it for the benefit of Canadians. While the PMPRB exists to promote the purpose of ensuring that the prices of patented medicines are not excessive, the goal of encouraging innovation and access must also be promoted. If this overarching goal is overlooked, innovative medicines, particularly orphan drugs that have no incentivization system, will not be made available for the benefit of Canadian patients.

Horizon has been Denied Procedural Fairness and Transparency

65. Horizon has been denied procedural fairness throughout its dealings with Board Staff:

(a) ***Board Staff ignored its own Guidelines:*** The Board has previously recognized the importance of the Excessive Price Guidelines, given the broad framework provided by section 85 of the *Act*. The Board has also acknowledged the important procedural fairness role that the Guidelines play: first, the Guidelines serve a notice function to the pharmaceutical industry and health care stakeholders as to the tests that will be applied by Board Staff to the pricing of

patented medicines; and second, it is important as a matter of fairness that all patentees are treated consistently and that there be stability in the principles governing the pricing of patented medicines. Notwithstanding the importance of the Guidelines and the Board's recognition that fairness requires that they ensure that consistent and stable principles are applied to the pricing of patented medicines, Board Staff has ignored the Guidelines in its Statement of Allegations and throughout its negotiations with Horizon.

(b) ***HDAP prejudged Horizon's case:*** As described in detail below, HDAP had pre-determined the issues before it, in that: (i) two of HDAP's members, in their capacity as members of CADTH, had already determined that PROCYSBI® should be subject to a price reduction; (ii) HDAP started its review/deliberations before it had received Horizon's new medicine submission.

(c) ***No notice of the methodology deployed in Board Staff's Notice of Allegations:*** Board Staff's unjustified departure from the Guidelines is compounded by its Notice of Allegations, which provide three previously undisclosed potential methodologies by which to calculate the non-excessive price of PROCYSBI®. These *ad-hoc* calculations have no grounding in the Guidelines, in Board Staff's public presentations, or prior dealings with other patentees, and Board Staff's Notice of Allegations provides no means of verifying them.

(d) ***Board Staff has displayed an animus against PROCYSBI®:*** Despite Horizon's many attempts to negotiate the pricing of PROCYSBI® (including an offer which would give Canada the lowest international price in the PMPRB7), Board Staff has refused to engage in good faith negotiations with Horizon. Board Staff's *animus* against Horizon is demonstrated by inflammatory public statements made by Board Staff's Executive Director, Doug Clark, about the price of PROCYSBI® in public testimony before the House of Commons Standing Committee on Health, on November 6, 2018: "The actual ratio between the price of Cystagon and the price of PROCYSBI® is even more outrageous, I would say."

66. Board Staff's dealings with Horizon in relation to PROCYSBI® are set out in detail below.

67. On December 5, 2017, Horizon (through its Canadian subsidiary, HZNP Therapeutics Canada Limited), submitted its Form 1 for each of 25 mg and 75 mg strength of delayed-release capsules of PROCYSBI®.

68. On January 30, 2018, Horizon submitted its new medicine submission to the PMPRB. The submission sought breakthrough status for PROCYSBI®. An Appendix to the submission listed the Phase III and extension studies, the pharmacokinetic and bioequivalence studies, and the ongoing studies conducted by Horizon.

69. On February 15, 2018, Board Staff prepared a New Medicine Scientific Staff Summary that proposed a series of questions to HDAP, including the use of Cystagon as a comparator. The authorship of the New Medicine Scientific Staff Summary is not known.

70. On February 26, 2018, HDAP prepared a report entitled, "New Medicine Review," the authorship of which is not known, as Board Staff has not shared the authorship of that report with Horizon.

71. The HDAP is a committee that meets four times a year. In 2018, it had regularly scheduled meetings in, among other dates, February and May. The HDAP included, among others, Dr. Peter Jamieson and Dr. Adil Virani, each of whom served on the Canadian Drug Expert Committee of CADTH, discussed further in paragraph 79(f) below). CADTH decided on December 13, 2017 that PROCYSBI® should be recommended provided that it be subject to a price reduction.

72. On February 26, 2018, Board Staff or HDAP prepared a document entitled "HDAP New Medicine Review," in which the questions posed in Board Staff's February 15, 2018 report appear to be answered by HDAP, namely:

(a) that PROCYSBI® be classified as a moderate improvement over Cystagon based on secondary factors; and

(b) that Cystagon be used as an appropriate comparator.

73. The HDAP reviewed PROCYSBI® at its meeting of February 26, 2018. On March 13, 2018, Board Staff alerted Horizon that HDAP had considered PROCYSBI® at its meeting of

February 26, 2018 and provided copies of HDAP, Board Staff and DIC reports. They also attached a letter dated March 13, 2018 from Board Staff regarding the introductory price review of PROCYSBI®.

74. On March 13, 2018, Board Staff issued a letter to Horizon indicating that Board Staff had commenced an investigation into the price of PROCYSBI®. Board Staff also indicated to Horizon that it had received a complaint regarding the price of PROCYSBI®, although Board Staff did not at that time reveal the identity of the complainant.

75. In its March 13, 2018 letter, Board Staff stated:

(a) that HDAP had classified PROCYSBI® as a "moderate improvement" based on secondary factors (as HDAP had determined PROCYSBI® should be classified as "slight or no improvement");

(b) it had conducted midpoint and highest international price comparison tests (the midpoint between the top of the therapeutic class comparison test and the Median International Price comparison test) establishing maximum average potential prices (MAPPs) under the Guidelines;

(c) in view of the substantial price differential between PROCYSBI® and its alleged comparator, Cystagon, the test as articulated in the Guidelines would not be applied, and proposed a MAPP of $5.3188 per 25 mg capsule and a MAPP of $15.9561 per 75 mg capsule;

(d) it had received a complaint regarding the price of PROCYSBI®, although Board Staff did not at that time reveal the identity of the complainant; and

(e) it had commenced an investigation into PROCYSBI®.

76. On March 28, 2018, Horizon provided a response to Board Staff's letter dated March 13, 2018, requesting HDAP to reconsider its characterization of PROCYSBI® as a "moderate improvement" and designation of Cystagon as a comparator. The response also included a copy of an August 1, 2017 CADTH Common Drug Review Patient Input Report demonstrating the real-world impact of PROCYSBI® on patients' lives and the impact of delayed release capsules on compliance.

77. On April 20, 2018, Horizon provided a further Request for Consideration to Board Staff. Seven days later, on April 27, 2018, Board Staff authored a New Medicine Review – Issue Paper for the purpose of asking HDAP whether Horizon's submissions of March 28, 2018 and April 20, 2018 changed HDAP's recommendations. In this April 27, 2018 paper, Board Staff advised HDAP that:

(a) "… Board Staff is required to consider the sale of Cystagon in Canada…"; and

(b) "Cystagon may be considered a comparator to Procysbi."

In so doing, Board Staff unduly influenced the outcome of HDAP's deliberations. Because HDAP will not meet with patentees, that process is opaque to patentees like Horizon.

78. On May 18, 2018, HDAP's conclusions (that there would be no changes to its initial recommendations) were provided to Horizon. The May 18 letter attached a copy of HDAP and Board Staff reports denying the request for reconsideration. Horizon denies the relevance of HDAP Report, as well as the other internal reports generated by Board Staff. Evidence concerning how Board Staff reached its own conclusion as to the proper non-excessive price of PROCYSBI® is irrelevant and should be given no weight by the Board.

79. On June 20, 2018, Board Staff provided an excerpt from the Newfoundland formulary from October 2017, the only month in which a price was reported in the formulary for Cystagon, which Board Staff used to conduct the TCC test for the introductory price for PROCYSBI® (as set out above, Newfoundland has never had any cystinosis patients). Board Staff stated that they "remain[ed] of the view that section 85(1) of the *Patent Act* requires Board Staff to consider Cystagon as a comparator to Procysbi in a price review."

80. On July 30, 2018, Horizon sent an email to PMPRB disputing that the Newfoundland formulary price for Cystagon was "public." Horizon also noted that Cystagon was not used as a comparator in other countries where the pricing for PROCYSBI® had been reviewed and approved. Horizon disputed that data relied upon by Board Staff for international pricing for PROCYSBI® was actual ex-factory pricing for PROCYSBI®. Horizon continues to dispute that it is appropriate to use the Newfoundland formulary price for Cystagon in determining the non-excessive price of PROCYSBI®.

81. PMPRB departed from its Guidelines and established policies and practices, in using a medicine, Cystagon, for which there is no publicly available price as a comparator. Where an SAP drug is a potential comparator, PMPRB's long-standing practice has been to use the Median International Price to set the MAPP due to lack of publicly available prices. Using a medicine sold under SAP is inappropriate as a comparator, as the manufacturer has discretion whether to charge for the SAP medicine and, if it does so charge, to determine how much to charge.

82. Many months later, on November 14, 2018, Horizon contacted Board Staff asking for an update and offering to meet with Board Staff to provide an update on the public listings of PROCYSBI® for all provinces in Canada. The next day, Board Staff responded that it remained of the view that the pricing was excessive and giving Horizon the opportunity to submit a voluntary compliance undertaking (VCU) to reduce the prices of PROCYSBI® and to offset excess revenues accrued. Absent a VCU, Board Staff intended to recommend that the Chairperson of the PMPRB issue a Notice of Hearing.

83. On December 6, 2018, Horizon met with Board Staff to present its draft VCU. The draft VCU proposed a price amongst the lowest in the world for both the 25 mg and 75 mg delayed-release capsules.

84. At the meeting of December 6, 2018, Board Staff requested that Horizon implement a 75% price reduction of the median international ex-factory list price (using the purported price of Cystagon as a comparator), failing which it would commence a hearing. Board Staff did not refer to its Guidelines in arriving at its proposed 75% price reduction. Board Staff came to that meeting empty handed (with Board Staff members bringing no pens or papers to record notes), declined to review a draft VCU that Horizon had prepared, and was unwilling to have a discussion with Horizon about pricing, despite Horizon's commitment to offer Canadians a price for PROCYSBI® that was amongst the lowest in the world. The meeting lasted approximately 10 minutes.

85. On January 14, 2019, the PMPRB issued its Notice of Hearing and provided a copy of the allegations of Board Staff.

86. At no time between May 18, 2018 and the commencement of the hearing did Board Staff show any willingness to discuss, in an open and transparent manner, the pricing of PROCYSBI® other than to insist that Horizon lower the median international ex-factory price of PROCYSBI® by 75% of the median international ex-factory price and to a level closer to what Board Staff had asserted to be the public price of Cystagon, an unapproved drug which does not contain the patented features which make PROCYSBI® a breakthrough or substantial improvement drug.

87. Horizon has maintained that it would offer one of the lowest international prices for PROCYSBI®.

88. The pricing methodology detailed in the Statement of Allegations was not presented to Horizon, but was rather set out in the Statement of Allegations as three *ex-post facto* methods to justify Board Staff's conclusion that the non-excessive price of PROCYSBI® is that of Cystagon.

Detailed Response to Statement of Allegations

89. Horizon admits the allegations in paragraphs:

(a) 1, 4, 6 (to the best of Horizon's information and belief), 10, 11, 12, 16, 17, 18, 19, 20, 25, 26, and 30.

(b) 2 (although Horizon states that Board Staff has ignored the lifespan of nephropathic cystinosis patients, the difference in lifespan of patients taking Cystagon versus those taking PROCYSBI® and understates difficulties associated with treatment with cysteamine (including sleeplessness, GI distress, lack of compliance and the consequences arising from lack of compliance));

(c) 3 and 7 (although Horizon states that Board Staff has understated the vast differences between PROCYSBI® and Cystagon as medicines by virtue of the enteric-coated microspherized beads which provide a breakthrough patented medicine for cystinosis patients);

(d) 13 (although Horizon states that the inventions in the 531 and 770 Patents pertain to the medicine present in PROCYSBI®, namely enteric-coated microspherized core beads of cysteamine bitartrate); and

(e) 22 (although Horizon denies the characterization of Board Staff that the Guidelines may not be an appropriate implementation of the factors set out in section 85 of the *Act* and states that PROCYSBI® and Cystagon are clinically not equivalent: they are different medicines with different clinical outcomes – the differences generated by the patented inventions disclosed in the PROCYSBI® Patents).

90. With respect to paragraph 8, Horizon denies that there is "no therapeutic advantage" between PROCYSBI® and Cystagon. While each is used in the treatment of nephropathic cystinosis, Cystagon's use is not one that has received a notice of compliance from Health Canada and Cystagon is vastly inferior to PROCYSBI® in terms of clinical outcomes and clinical equivalency. The statement that "neither is inferior to the other" is a distorted conclusion borne out of the fact that the clinical trial that formed the basis of approval in the United States is a "non-inferiority" study, and that which was required to support the approval in the United States. It is not correct to say, as Board Staff suggests in the Statement of Allegations, that PROCYSBI® is no better than Cystagon. The purpose of the study was to study whether it was non-inferior, which is all that was required. An assessment of all studies and literature clearly demonstrates that PROCYSBI® is clearly superior to Cystagon.

91. With respect to paragraph 8, PROCYSBI® was approved in the United States under a 505(b)(2) regulatory pathway, which is a New Drug Application ("NDA"). The 505(b)(2) NDA is one of three U.S. Food and Drug Administration (FDA) drug approval pathways created, in part, to help avoid unnecessary duplication of studies already performed on a previously approved ("reference" or "listed") drug; the section gives the FDA express permission to rely on data not developed by the NDA applicant. A 505(b)(2) NDA contains full safety and effectiveness reports but allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant. This can result in a much faster route to approval, compared with a traditional development path, while creating new, differentiated products with tremendous commercial value. This faster route to approval is particularly important for orphan drugs. PROCYSBI® was first approved in this fashion, in the United States, in 2013 for the treatment of nephropathic cystinosis in patients aged 6 years and older. The indication for PROCYSBI® was

extended in 2015 to include patients 2 years and older and most recently in 2017 to include patients aged 1 year and older.

92. With respect to paragraph 9, and the allegation that the *adult* dose of PROCYSBI® is 1,500 mg, the dosing of PROCYSBI® is based on the weight of the patient and involves both the determination of a starting dose and the determination of a maintenance dose. While it is correct that PROCYSBI® is indicated for adults, most uses of PROCYSBI® will be in children and the dose will be less than 1,500 mg per day, which will reflect a lower cost than that presented by Board Staff in paragraph 10.

93. With respect to paragraph 23, Horizon states that Board Staff presented limited information to Horizon regarding the pricing information it had on PROCYSBI® and Cystagon. Horizon states that Board Staff has withheld information with respect to pricing and sales information and demands production of all information Board Staff has with respect to pricing, market share, availability and extent of sales of PROCYSBI® and Cystagon in Canada, in any of the PMPRB7 countries and elsewhere.

94. With respect to paragraph 24, Board Staff refused to receive any VCU other than one that resulted in a price reduction of 75% – that is, 25% of the price of PROCYSBI®. Horizon states that, at all times, Board Staff was intent on recommending the issuance of a Notice of Hearing.

95. With respect to paragraph 27, Horizon states that PROCYSBI® and Cystagon are not the same medicine and denies that the "medicine" for the purposes of the *Act* is cysteamine bitartrate. The medicine for the purposes of the *Act* is that to which the invention pertains – namely enterically coated, microspherized core beads of cysteamine bitartrate. PROCYSBI® is the only medicine utilizing the patented inventions.

96. With respect to paragraphs 28 and 29, Horizon states that PROCYSBI® and Cystagon are not equivalent forms of cysteamine and denies that Cystagon has been made available in Canada. Horizon accepts Boards Staff's admission that there are no other medicines in the same therapeutic class.

97. With respect to paragraph 29, Horizon denies that Cystagon is in the same therapeutic class as PROCYSBI®. Alternatively, to the extent that it is, PROCYSBI® is a substantial

improvement over Cystagon by virtue of the patented medicine in PROCYSBI®, namely enterically coated, microspherized core beads of cysteamine bitartrate, the subject of the PROCYSBI® Patents.

98. With respect to paragraph 35, Horizon denies that the Guidelines ought to be discarded and denies that the circumstances of this specific case are so unusual as to warrant abandoning the Guidelines. The Guidelines should be applied, as discussed above, to arrive at the Median International Price for PROCYSBI®. To the extent that the circumstances of this specific case are unusual, those factors should point in favour of endorsing an orphan drug manufacturer commercializing a patented medicine in Canada that has no comparator, for the benefit of the relatively small number of Canadians suffering from this disease.

99. With respect to paragraph 36, Horizon denies that PROCYSBI® is to be categorized as a "slight or no improvement" drug. It is a drug which will increase efficacy through increased compliance, as well as reducing the significant side effects experienced with cysteamine treatment. It provides life-saving and life-extending relief for cystinosis sufferers.

100. With respect to paragraphs 37 and 38, Horizon denies that the test to be applied in determining whether a new product provides moderate improvement was "originally developed in the context of relatively small differences in prices between a new drug and its comparators" such as the "one to two-fold difference in prices that resulted when the mid-point test was developed."

101. With respect to paragraph 39, which is improper speculation, Horizon denies manipulating the price of PROCYSBI® in this fashion. Paragraph 39 is scandalous and ought to be ignored.

102. With respect to paragraph 41, Horizon denies Board Staff's three alternative approaches and states that these approaches, presented for the first time in the Statement of Allegations, constitute a radical and perverse departure from the Guidelines and the factors under section 85, including for the following reasons:

(a) With respect to the so-called "Same Medicine Comparison" Test described in paragraphs 42 to 45, Horizon denies that "PROCYSBI® is Cystagon" or that PROCYSBI® differs from Cystagon only in its release characteristics;

(b) With respect to the so-called "Market Share Comparison" Test described in paragraphs 46 to 53, Horizon states that Board Staff has failed to provide it with any of the data upon which it relies in arriving at the stated conclusions and further denies that the reformulation of the cysteamine bitartrate into enterically-coated microspherized core beads, results in a product that is of minor value, especially in view of the following:

(i) the fact that Cystagon was never and is still not approved in Canada, depriving Canadian physicians and patients of French and English labelling, product monographs, instructions for use and other safety, quality, and efficacy information required to be filed and updated with Health Canada to support a marketing authorization;

(ii) the fact that Cystagon, approved by regulatory authorities other than Health Canada and available for over 20 years, was never studied by its manufacturer to determine whether it could be delivered or dosed differently to improve compliance, yet was only available in immediate-release formulation, notwithstanding the impediment to compliance and negative health consequences (including grievous gastrointestinal adverse effects) caused by the immediate-release formulation;

(iii) the extensive testing by the inventors which resulted in not only a patent but a breakthrough in clinical outcomes, which has been confirmed by other investigators;

(iv) that Health Canada itself recognized PROCYSBI® as a breakthrough by:

(A) fast-tracking the PROCYSBI® regulatory submission;

(B) recognizing PROCYSBI® as an "innovative medicine" and awarding it 8.5 years of data protection;

(C) requiring that PROCYSBI® be approved by a "new drug submission," not an "abbreviated new drug submission" which is the regulatory pathway required for medicines which are the same).

(c) With respect to the so-called "Market Share Comparison" Test, assuming it were to have application (which it does not):

(i) there is no reason to exclude Germany from consideration;

(ii) PROCYSBI® does not have approval for use in children less than one year old (which accounts for certain of the Cystagon market share, as it is used in children less than one year old, on a SAP basis).

(d) With respect to the so-called "Premium Comparison" Test, Horizon denies the application of this test and further states that the setting of the standard as "the quarter-point between the prices of Cystagon and the current price of PROCYSBI®" is arbitrary, with no foundation in the *Act* or the Guidelines.

103. With respect to paragraph 47, and the allegation that the availability of Cystagon for Canadians with nephropathic cystinosis was curtailed, Horizon states that any curtailment is as a result of a decision made by the delegates of the Minister of Health at Health Canada. The decision to make or not make Cystagon available via the SAP, because of the approval of PROCYSBI® or otherwise, is not a decision made, or influenced in any way, by Horizon. It is not Horizon's intent to hinder or in any way prevent patient access to Cystagon.

104. With respect to paragraph 58, Horizon denies that PROCYSBI® offers no clinical therapeutic advantage or that "the only advantage is a reduction in the dosing schedule, which *may* result in increased compliance rates." Horizon states that PROCYSBI® has therapeutic advantages and improved clinical outcomes;

105. With respect to paragraph 59, Horizon denies that other health agencies in other countries have, like CADTH, recommended only listing PROCYSBI® at a significantly reduced price. This allegation lacks specificity and particularity of any material facts.

106. With respect to paragraph 63, Horizon and its predecessors have expended tremendous resources, funds and efforts in the research and development of PROCYSBI®.

107. With respect to paragraph 65, Horizon denies that "a review of the Canadian publicly available prices of modified-releases formulations … are generally priced at a level that is either the same or a relatively small percentage above the price of their immediate release counterparts" and states that Board Staff have failed to particularize this statement with any material facts, which, if available, would show how inappropriate such a statement is in view of the specific facts of this case and orphan drug development.

Procedural Relief

108. Horizon will seek disclosure, by motion if necessary, of:

(a) Board Staff's investigative file so as to understand the position of Board Staff that ought to have been transmitted to Horizon;

(b) documents upon which Board Staff intends to rely; and

(c) particulars of allegations that are not supported by material facts.

109. Horizon reserves the right to identify, mark and file documents with the Board marked "CONFIDENTIAL/CONFIDENTIEL" in accordance with Rule 14(6).

Relief Requested

110. Horizon requests that this application be dismissed.

February 18, 2018

Original signature redacted

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