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

AMENDED STATEMENT OF ALLEGATIONS OF BOARD STAFF

Introduction

1. This Statement of Allegations results from an investigation by Board Staff into the price of Procysbi, a drug containing the patented medicine cysteamine bitartrate. Procysbi is sold in Canada by HZNP Therapeutics Canada Ltd. doing business as Horizon Therapeutics Canada ("Horizon"). Procysbi is sold in Canada in the form of 25mg and 75mg oral capsules (respectively, DIN 02464705 and 02464713).

Procysbi

2. Procysbi is indicated for the treatment of the rare and life-long multisystem genetic disorder nephropathic cystinosis. Among other symptoms, nephropathic cystinosis impairs the filtering function of the kidney, eventually progressing to kidney failure and necessitating a kidney transplant. Treatment with cysteamine bitartrate significantly delays the need for kidney transplant and substantially increases patients' lifespans, even after transplant.

3. The only active medicinal ingredient in Procysbi is cysteamine bitartrate. The cysteamine in Procysbi is in microspherized core beads that are enteric-coated

and encapsulated. As a result, Procysbi is a modified release oral capsule that is taken every twelve (12) hours. (**Attachment 1**)

4. Health Canada issued a Notice of Compliance for Procysbi on June 13, 2017. (**Attachment 2**) The first sale of Procysbi in Canada was on September 7, 2017.

Cystagon

5. Cystagon is the trade name for another product containing, as its only active medicinal ingredient, cysteamine bitartrate, and as such, cysteamine bitartrate sold as Cystagon is both the same medicine and a medicine in the same therapeutic class as cysteamine bitartrate sold as Procysbi.

6. Cystagon is manufactured by the company Mylan Pharmaceuticals Inc. Cystagon was commercialized in Europe by Orphan Europe (a Recordati group company) under license from Mylan. As of April 2018, Mylan entered into an agreement for the acquisition of the rights to Cystagon for certain territories, including Europe. Cystagon is marketed in the United States by Mylan.

7. Like Procysbi, the only active medicinal ingredient in Cystagon is cysteamine bitartrate. However, unlike Procysbi, the cysteamine in Cystagon is not in microspherized core beads that are enteric-coated and encapsulated. As a result, unlike Procysbi, Cystagon is an immediate release oral capsule, not a modified release oral capsule, and therefore, Cystagon must be taken every six (6) hours rather than every twelve (12) hours. Like Procysbi, Cystagon is indicated for the treatment of nephropathic cystinosis.

8. Procysbi and Cystagon both contain the same single medicinal ingredient (cysteamine bitartrate). In addition, the mechanism of action for both Procysbi and Cystagon is identical. Both Procysbi and Cystagon deplete the cystine that accumulates and crystallizes in the tissues of the body, as a result of nephropathic cystinosis. Moreover, the same indications and contraindications exist for both Procysbi and Cystagon, reflecting the fact that they utilize the identical active ingredient. There is no therapeutic advantage between Procysbi

and Cystagon: neither is inferior to the other in terms of the efficacy of treatment, and both lead to the same therapeutic outcome. In the United States, Procysbi was approved under a 505(b)(2) regulatory pathway that relied upon the safety and effectiveness of Cystagon (NDA 020392) as a reference listed drug.

9. Cystagon has been marketed internationally for many years, and, for example, was approved for sale in the United States in 1994. Cystagon is not approved or marketed in Canada, though it has been made available for sale in Canada for over two decades through the Special Access Programme ("SAP") maintained pursuant to C.08.010 and C.08.011 of the *Food and Drug Regulations,* C.R.C., c. 870 ("*Food and Drug Regulations*"). Cystagon is fully approved for sale in the comparator countries ("the Comparator Countries"), which are listed in the Schedule of the *Patented Medicines Regulations,* SOR/94-688 ("Regulations").

The Patents

10. Canadian Patent No. CA2640531 is entitled "Enterically coated cysteamine, cystamine and derivatives thereof." It was issued on January 3, 2017. It is owned by the Regents of the University of California and licensed to Horizon. (**Attachment 3**)

11. Canadian Patent No. CA2914770 is entitled "Delayed release cysteamine bead formulation, and methods of making and using same." It was issued on September 27, 2016. It is owned by Horizon. (**Attachment 4**)

12. Horizon is, for the purposes of the Patented Medicine Prices Review Board ("The Board") considered a patentee, as defined in ss.79(1) of the Act, because Horizon is entitled to the benefit of the 2,640,531 and 2,640,531 patents.

13. Moreover, pursuant to s.3(1)(h) of the Patented Medicines Regulations, Horizon filed a "Form 1" with the PMPRB where it admitted that the inventions in the 2,640,531 and 2,640,531 patents pertain to the medicine present in Procysbi (i.e., cysteamine bitartrate), and that it is a person entitled to the benefits of a patent or to exercise any rights in relation to a patent.

The Annual Cost of the Medicine

14. The total daily dose of cysteamine bitartrate for an adult patient taking it either in the form of Cystagon or Procysbi is the same, namely 1,500 mg.

15. For a single adult patient with nephropathic cystinosis, the annual cost of cysteamine therapy in Canada is approximately $325,000 per year for the drug Procysbi (based on Procysbi's introductory list price) or approximately $5,000 per year for the drug Cystagon (priced at the time of Procysbi's introduction). In either case, cysteamine therapy must begin as soon as the condition is first diagnosed (often before two years old) and continue for the entire life of the patient.

The SAP

16. The SAP provides access to drugs, like Cystagon, that cannot otherwise be sold or distributed in Canada. Specifically, the SAP provides an exemption from the *Food and Drugs Act*, R.S.C., 1985, c. F-27, and its *Food and Drug Regulations*. However, in order to be granted this exemption, there must be a medical emergency: a serious or life-threatening condition where conventional therapies have been considered and ruled out, have failed, are unsuitable or unavailable.

17. Access to drugs under the SAP is discretionary and granted on a case-by-case basis. Among the factors considered when deciding whether to grant a request under the SAP is the availability of marketed alternatives, since the SAP is not a means to circumvent regulatory review of a submission for marketing a drug in Canada. The SAP does not take into consideration the cost of marketed alternatives.

18. When the Notice of Compliance was issued for Procysbi allowing it entry into the Canadian market, Procysbi became a marketed alternative to Cystagon for patients with nephropathic cystinosis. Therefore, the SAP severely restricted access to Cystagon. Patients who were previously receiving cysteamine therapy

in the form of Cystagon can only continue to do so if a medical practitioner establishes that the patient is medically unable to use Procysbi.

The Regulatory Filings

19. Horizon received a Notice of Compliance for Procysbi on June 13, 2017 and the first sale of Procysbi in Canada took place on September 7, 2017. Pursuant to s. 3(3)(a) of the Regulations, Horizon should have filed the information set out in s. 3(1)(a) of the Regulations by June 20, 2017. Horizon did not file the information by that date. Board Staff subsequently contacted Horizon and, following the request of Board Staff, Horizon filed the required Form 1 on December 5, 2017, and subsequently filed price and sales information for the period between July 2017-December 2017 at the end of January, 2018 and for the period between January 2018-July 2018 on July 30, 2018.

The Board Staff Investigation

20. Following review of Procysbi by the Human Drug Advisory Panel ("HDAP"), Board Staff automatically commenced an investigation into the introductory price of Procysbi on March 13, 2018, pursuant to the investigation criteria in the Compendium of Policies, Guidelines and Procedures ("the *Guidelines*").

21. Board Staff also received a complaint, dated February 22, 2018, about the price of Procysbi from the pan-Canadian Pharmaceutical Alliance ("pCPA"). Receipt of a complaint is also an automatic investigation trigger under the *Guidelines*.

22. Upon the commencement of the investigation into Procysbi, Horizon was notified that Board Staff believed that the tests set out in the *Guidelines* may not be an appropriate implementation of the factors set out in s. 85 of the *Act* under the unusual circumstances of this case. In particular, Board Staff expressed serious concern about the extreme price differential between Procysbi and Cystagon in view of the fact that Procysbi and Cystagon contain the same medicinal ingredient and are approved for the same indications.

23. The investigation by Board Staff compared the National Average Transaction Price ("N-ATP") of Procysbi to the publicly available list price of Cystagon in Canada. Board Staff also reviewed *inter alia* the prices of Procysbi and Cystagon in the Comparator Countries. Board Staff also reviewed data regarding the volume of sales of Procysbi and Cystagon in the Comparator Countries.

24. Board Staff informed Horizon that the price of Procysbi appeared to be excessive. Horizon did not lower its price or submit an acceptable VCU. Therefore, as per the procedure described in s. C.13.6 of the *Guidelines,* Board Staff referred the matter to the Chairperson and recommended the issuance of a Notice of Hearing.

The s. 85 Factors

25. Subsection 85(1) of the *Act* states the following:

> In determining under section 83 whether a medicine is being or has been sold at an excessive price in any market in Canada, the Board shall take into consideration the following factors, to the extent that information on the factors is available to the Board:
>
> (a) the prices at which the medicine has been sold in the relevant market;
>
> (b) the prices at which other medicines in the same therapeutic class have been sold in the relevant market;
>
> (c) the prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada;
>
> (d) changes in the Consumer Price Index; and
>
> (e) such other factors as may be specified in any regulations made for the purposes of this subsection.

26. To date, no additional factors have been specified by regulation for the purposes of subsection 85(1) of the *Act*.

85(1)(a) The Price at which the medicine has been sold in the Relevant Market in Canada and in countries other than Canada

85(1)(c) The Prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada

27. "The medicine" under paras. 85(1)(a) and 85(1)(c) is cysteamine bitartrate. This is the only active medicinal ingredient in Procysbi and Cystagon. As a result, while Procysbi and Cystagon are different finished drugs sold under different trade names, they are the same medicine under the Act, because their only active medicinal ingredient is the same.

85(1)(b) The prices at which other medicines in the same therapeutic class have been sold in the relevant market

85(1)(c) The prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada

28. Cysteamine is the only target-specific medicine for cystinosis. Procysbi and Cystagon are the only forms of cysteamine available in Canada. Consequently, there are no other medicines in the same therapeutic class.

29. Therefore, in addition, or in the alternative, Cystagon is in the same therapeutic class as Procysbi, as it also treats the same indication (i.e., nephropathic cystinosis) and it also utilizes the same single active medicinal ingredient (cysteamine bitartrate) in the same treatment mechanism (i.e., it depletes the accumulated cystine in the patient's tissues).

85(1)(d) Changes in the Consumer Price Index

30. This factor has no relevance to the determination of whether the price of Procysbi was excessive at the time of its first sale. In addition, the price of Procysbi has

not changed since introduction and the CPI inflation rate in 2017 (*i.e.* inflation from January 1, 2017 to December 31, 2017) was minimal (1.6%).

Price Information for cysteamine bitartrate

31. The publicly available ex-factory prices at which cysteamine bitartrate, under the trade names Procysbi and Cystagon, is sold in Canada and in the Comparator Countries are set out in the following tables:

(a) Ex-factory Procysbi Prices filed by Horizon in "Form 2" (converted to prices per mg)

Procysbi 25mg (2017-2)

Country	Price in domestic currency	Price in CAD$ (using 36mo. Rolling exchange rates) (Apr 2017)	Price in CAD$ (using 36mo. Rolling exchange rates) (Dec 2017)
Canada	**0.4140 (CDN$)**	**0.4140 (CDN$)**	**0.4140 (CDN$)**
France	No price filed	NA	NA
Germany	**0.2902 (EURO)**	**0.4179 (CDN$)**	**0.4207 (CDN$)**
Italy	No price filed	NA	NA
Sweden	No price filed	NA	NA
Switzerland	No price filed	NA	NA
United Kingdom	**0.2240 (GBP)**	**0.4115 (CDN$)**	**0.4049 (CDN$)**
United States	**3.3402 (USD)**	**4.2136 (CDN$)**	**4.3449 (CDN$)**

Procysbi 25mg (2018-1)

Country	Price in domestic currency	Price in CAD$ (using 36mo. Rolling exchange rates) (Jun 2018)
Canada	**0.4140 (CDN$)**	**0.4140 (CDN$)**
France	No price filed	NA
Germany	**0.2902 (EURO)**	**0.4289 (CDN$)**
Italy	No price filed	NA
Sweden	No price filed	NA
Switzerland	No price filed	NA
United Kingdom	**0.2240 (GBP)**	**0.4003 (CDN$)**
United States	**3.3402 (USD)**	**4.3687(CDN$)**

Procysbi 75mg (2017-2)

Country	Price in domestic currency	Price in CAD$ (using 36mo. Rolling exchange rates) (Apr 2017)	Price in CAD$ (using 36mo. Rolling exchange rates) (Dec 2017)
Canada	**0.4140 (CDN$)**	**0.4140 (CDN$)**	**0.4140 (CDN$)**
France	No price filed	NA	NA
Germany	**0.2902 (EURO)**	**0.4179 (CDN$)**	**0.4207 (CDN$)**
Italy	No price filed	NA	NA
Sweden	No price filed	NA	NA
Switzerland	No price filed	NA	NA
United Kingdom	**0.2240 (GBP)**	**0.4115 (CDN$)**	**0.4049 (CDN$)**
United States	**1.1134 (USD)**	**1.4045 (CDN$)**	**1.4483 (CDN$)**

Procysbi 75mg (2018-1)

Country	Price in domestic currency	Price in CAD$ (using 36mo. Rolling exchange rates) (Jun 2018)
Canada	**0.4140 (CDN$)**	**0.4140 (CDN$)**
France	No price filed	NA
Germany	**0.2902 (EURO)**	**0.4289 (CDN$)**
Italy	No price filed	NA
Sweden	No price filed	NA
Switzerland	No price filed	NA
United Kingdom	**0.2240 (GBP)**	**0.4003 (CDN$)**
United States	**1.1134 (USD)**	**1.4562 (CDN$)**

(b) Publicly-Available Ex-Factory Cystagon Prices (in price per mg)

Cystagon 150mg

Country	Price in domestic currency	Price in CAD$ (using 36mo. Rolling exchange rates) (Apr 2017)	Price in CAD$ (using 36mo. Rolling exchange rates) (Dec 2017)
Canada	**0.0077 (CND$)**	**0.0077 (CND$)**	**0.0077 (CND$)**
France	**0.0129 (EURO)**	**0.0186 (CDN$)**	**0.0187 (CDN$)**
Germany	**0.0177 (EURO)**	**0.0255 (CDN$)**	**0.0257 (CDN$)**
Italy	**0.0093 (EURO)**	**0.0134 (CDN$)**	**0.0135 (CDN$)**
Sweden	**0.1356 (SEK)**	**0.0208 (CDN$)**	**0.0207 (CDN$)**

Switzerland	NA	NA	NA
United Kingdom	**0.0127 (GBP)**	**0.0233 (CDN$)**	**0.0230 (CDN$)**
United States	**0.0080 (USD)**	**0.0101 (CDN$)**	**0.0104 (CDN$)**

Cystagon 50mg

Country	Price in domestic currency	Price in CAD$ (using 36mo. Rolling exchange rates) (Apr 2017)	Price in CAD$ (using 36mo. Rolling exchange rates) (Dec 2017)
Canada	NA	NA	NA
France	**0.0138 (EURO)**	**0.0199 (CDN$)**	**0.0200 (CDN$)**
Germany	**0.0225 (EURO)**	**0.0324 (CDN$)**	**0.0326 (CDN$)**
Italy	**0.0095 (EURO)**	**0.0137 (CDN$)**	**0.0138 (CDN$)**
Sweden	**0.1360 (SEK)**	**0.0209 (CDN$)**	**0.0208 (CDN$)**
Switzerland	NA	NA	NA
United Kingdom	**0.0140 (GBP)**	**0.0257 (CDN$)**	**0.0253 (CDN$)**
United States	**0.0082 (USD)**	**0.0103 (CDN$)**	**0.0107 (CDN$)**

Application of the s. 85(1) Factors

32. Board Staff submits that the proper application of the s. 85(1) factors in the unique circumstances of this case, where a regulatory regime (namely, the SAP) has severely limited access to the only alternative, leads to the conclusion that the price of Procysbi in Canada has been excessive from the time of its introduction because it exceeds the publicly available list price of Cystagon ("the Same Medicine Comparison") in Canada and in the Comparator Countries. Consequently, the price of Procysbi should be lowered so that it does not exceed the publicly available list price of Cystagon in Canada and in the Comparator Countries at the time of introduction in Canada.

33. In the alternative, the price of Procysbi in Canada has been excessive from the time of its introduction because, based on an analysis of the market share of Procysbi and Cystagon in the Comparator Countries where competitive forces are operative between the two drugs, i.e., where regulation does not restrict the

availability of Cystagon as the SAP does in Canada ("the Market Share Comparison"), the price of Procysbi exceeds the market-share adjusted price ("Market Share Price") in the Comparator Countries. Consequently, the price of Procysbi should be lowered so that it does not exceed the Market Share Price.

34. In the further alternative, the price of Procysbi in Canada has been excessive from the time of its introduction because it exceeds the price that results if a reasonable premium is added above the price of Cystagon in Canada/Comparator Countries to account for the potential additional benefit of the addition of an enteric coating to the same single active medicinal ingredient ("the Premium Comparison"). Consequently, the price of Procysbi should be lowered so that it does not exceed the publicly available list price of Cystagon in Canada and in the Comparator Countries at the time of introduction in Canada, plus a reasonable premium (the "Premium Price").

The *Guidelines*

35. Board Staff further submits that the applicable tests set out in the *Guidelines* are not binding on the Board, Board Staff, or the patentee, and that a strict application of the comparison methodologies used in those tests is not an appropriate implementation of the Act in this case unless they are modified to account for the unusual circumstances of this specific case.

36. Section c. 11.7 of the *Guidelines* provides that the introductory price of a new product that provides slight or no improvement will be potentially excessive if its N-ATP exceeds the domestic TCC Test (Schedule 3).

37. Section c. 11.5 of the *Guidelines* provides a different test where the introductory price of a new product provides moderate improvement. Under this test, which was originally developed in the context of relatively small differences in prices between a new drug and its comparators, the new product's price is compared against the midpoint of the price between the median international price

comparison ("MIPC") test and the highest non-excessive price of the comparator(s) on the TCC.

38. However, the application of this test can yield absurd results in cases where the new product's price is substantially higher than the comparator or is set at an artificially high level. For example, the difference between the introductory price of Procysbi and Cystagon is approximately 54 fold, much higher than the one to two-fold difference in prices that resulted when the mid-point test was developed. As a result, if Procysbi were subjected to this test, it would result in the price of Procysbi being constrained to the midpoint (Schedule 5) – i.e. at a level that is over 27 times higher than the price of Cystagon.

39. This methodology is also vulnerable to artificial pricing. For example, by setting a medicine's public ex-factory prices artificially high in other countries while providing free access to patients to encourage them to switch drugs, it is possible to skew the midpoint in Canada beyond the actual value of the medicine if it were being sold instead of distributed for free. Similarly, having a very high "list price" in a country where a medicine is not being reimbursed (so little or no sales are taking place) is another way to skew the midpoint.

40. Finally, the methodology in the Guidelines test fails to adequately address the availability of Cystagon in countries other than Canada. Under the Guidelines test, the MIPC is calculated based on the price of Procysbi in the PMPRB 7 countries. However, s. 85(1)(c) of the Patent Act requires the Board to consider "the prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada", hence, the price of Cystagon in the PMPRB7 should be considered in this case.

41. For all these reasons, Board Staff submit that the following three alternative approaches, described in greater detail below, represent the best approaches to determining whether Procysbi has been sold at an excessive price.

(i) Alternative 1: The Same Medicine Comparison

42. Since Procysbi and Cystagon are the same medicine – cysteamine bitartrate – and are direct therapeutic comparators (same medicine for same indication), the proper application of the s. 85(1) factors should result in a price for Procysbi that does not exceed the publicly available ex-factory price of Cystagon in Canada and in the Comparator Countries. There is no reason why two products which contain the same medicinal ingredient and are indicated for the same condition in the same population should be priced differently. Both Procysbi and Cystagon have the same total maximum daily dosage, and the only relevant distinction between the two is that Cystagon is administered in 4 daily doses (one every six hours) and Procysbi is administered in 2 daily doses (one every twelve hours). Put simply, Procysbi is Cystagon, and differs only in its release characteristics.

43. Therefore, to the extent that the N-ATP of Procysbi exceeded the publicly available ex-factory price of Cystagon in Canada, Board Staff submits that Horizon has sold Procysbi at an excessive price. Comparing the price of Procysbi in Canada vs the price of Cystagon in the Comparator countries yields the same conclusion.

44. The application of the Same Medicine Comparison (Canada) shows that Horizon sold Procysbi at an excessive price and accumulated excess revenues as per the following tables:

Procysbi 25mg

Drug	Strength	Price (all Canada)	Maximum Dosage Regimen per day	Cost per day	"Same Medicine Comparison" result (using Canadian price for Cystagon)
Procysbi	25mg/capsule	$10.3500	60 Capsules	$621.0000	$0.1913
Cystagon	150mg/capsule	$1.1481	10 Capsules	$11.4810	

Procysbi 75mg

Drug	Strength	Price (all Canada)	Maximum Dosage Regimen per	Cost per day	"Same Medicine Comparison" result (using Canadian price

			day		for Cystagon)
Procysbi	75mg/capsule	$31.0500	20 Capsules	$621.0000	$0.5740
Cystagon	150mg/capsule	$1.1481	10 Capsules	$11.4810	

	Excess Revenues Same Medicine Comparison (using Canadian price for Cystagon)[1]
Procysbi 25mg	$76,190.25
Procysbi 75mg	$3,078,076.00
TOTAL	**$3,154,266.25**

45. The application of the Same Medicine Comparison (International) – using average international prices for Cystagon - yields similar results:

Drug	Strength	Price (Cystagon PMPRB 7)	Maximum Dosage Regimen per day	Cost per day	"Same Medicine Comparison" result (using average PMPRB7 price for Cystagon)
Procysbi	25mg/capsule	$10.3500	60 Capsules	$621.0000	$0.4649
Cystagon	150mg/capsule	$2.7896	10 Capsules	$27.8960	

Procysbi 75mg

Drug	Strength	Price (Cystagon PMPRB 7)	Maximum Dosage Regimen per day	Cost per day	"Same Medicine Comparison" result (using average PMPRB7 price for Cystagon)
Procysbi	75mg/capsule	$31.0500	20 Capsules	$621.0000	$1.3948
Cystagon	150mg/capsule	$2.7896	10 Capsules	$27.8960	

[1] Calculations of excess revenue are based, in part, on data from the filings of Horizon for 2017(2) and 2018(1).

	Excess Revenues Same Medicine Comparison (using average PMPRB7 price for Cystagon)[2]
Procysbi 25mg	$74,138.25
Procysbi 75mg	$2,995,175.20
TOTAL	$3,069,313.45

(ii) Alternative 2: The Market Share Comparison

46. In the alternative, and to the extent that Horizon argues, and this Board accepts, that the enteric coating in Procysbi should justify *some* higher price for Procysbi over Cystagon, Board Staff submits that the introductory price of Procysbi was excessive because the relatively minor value of the enteric coating does not justify the extreme difference between the prices of Procysbi and Cystagon. At best, a maximum non-excessive price for Procysbi in Canada that includes a premium for the value of the enteric coating should not be above the international market share adjusted price of Procysbi.

47. Due to the nature of the regulatory regime in Canada, once a Notice of Compliance was issued for Procysbi, the availability of Cystagon through the SAP for Canadians with nephropathic cystinosis was severely curtailed. As a result, instead of having to compete with Cystagon, Horizon essentially captured (or is in the process of capturing) the entire Canadian market of nephropathic cystinosis patients (with the limited exception of those who cannot tolerate Procysbi and may still access Cystagon through the SAP).

48. Since Canadians with nephropathic cystinosis no longer have the ability to use Cystagon through the SAP (without first demonstrating a clinical intolerance to Procysbi), they have no choice but to use Procysbi, a drug which is identical to Cystagon (save for its enteric coating and the consequent reduction in dosing

[2] Calculations of excess revenue are based, in part, on data from the filings of Horizon for 2017(2) and 2018(1).

regimen). Notwithstanding the therapeutic comparability of the two drugs, Procysbi costs almost sixty times the price of Cystagon.

49. Unlike the situation which prevails in Canada, Cystagon and Procysbi are both available in most of the Comparator Countries in the same way (i.e., they have the same level of regulatory approval). In this circumstance, Procysbi fails to capture the entire market share of patients who require cysteamine therapy in the Comparator Countries when it competes head-to-head with Cystagon. Procysbi is either too expensive and/or does not provide sufficient clinical benefits to displace Cystagon in these markets. Indeed, in a number of the comparator countries, Procysbi is either not covered by public or private insurance plans, or is only available on a limited coverage basis in view of the availability of the same medicine (Cystagon) at a substantially lower price. The only exception occurs in Germany, where a combination of regulatory anomalies resulted in reimbursement without price review. In Germany, orphan drugs like Procysbi are presumed to have an additional therapeutic benefit once they receive market authorisation, without reference to an appropriate comparator (like Cystagon), as long as annual statutory health insurance expenditure for the entire population treated with the drug (Procysbi) remains below EUR 50 million. In other words, because Germany does not expend more than EUR 50 million on Procysbi, no cost-effectiveness analysis was performed and Procysbi was reimbursed without regard to its price.

50. As a result, in countries where the price of Procysbi was a consideration for reimbursement decisions, there are very few (if any) sales of Procysbi at the publicly available list prices. This is also the case for the United States, where prices are un-regulated. It should be noted that, as per Horizon's filings, Procysbi is not sold at all in France, Italy, Switzerland or Sweden, meaning that the market share percentage of Cystagon if available in those countries can be assumed to be 100%.

51. Under this alternative, Board Staff submits that a proper application of the s. 85(1) factors should seek to replicate in Canada the competitive market situation that prevails in the Comparator Countries where there is no SAP affecting competition between the two drugs, and where Cystagon and Procysbi are both available to patients. Following such an approach would ensure that maximum expenditures on cysteamine bitartrate in Canada mirror maximum potential expenditures in the Comparator Countries where Procysbi faces competition from Cystagon. Board Staff submits that Germany should be excluded from the comparison due to the unusual market conditions there. However, even if Germany is included in the calculations, the price of Procysbi in Canada is still shown to be excessive.

52. The following tables set out the application of the Market Share Comparison (including Germany) and resulting excess revenues:

Drug	Unit Price	Price per mg	% Market Share average (includes Germany)	Price per mg weighted by share	Weighted price per mg combined	Result
Procysbi 25mg	$10.3500	$0.4140	~~18.25%~~ 18.24 %	$0.0756	$0.0819	$2.0475
Procysbi 75mg	$31.0500	$0.4140	~~18.25%~~ 18.24%	$0.0756	$0.0819	$6.1425
Cystagon 150mg	$1.1481	$0.0077	~~81.75%~~ 81.76%	$0.0063	--	--

	Excess Revenues Market Share Approach (calculation including Germany)[3]
Procysbi 25mg	$62,268.75
Procysbi 75mg	$2,515,657.50
TOTAL	**$2,577,926.25**

[3] Calculations of excess revenue are based, in part, on data from the filings of Horizon for 2017(2) and 2018(1).

53. The following tables set out the application of the Market Share Comparison (excluding Germany) and resulting excess revenues:

Drug	Unit Price	Price per mg	% Market Share average (Germany excluded)	Price per mg weighted by share	Weighted price per mg combined	Result
Procysbi 25mg	$10.3500	$0.4140	~~6.08%~~ 6.10%	~~$0.0252~~ $0.0253	~~$0.0324~~ $0.0325	~~$0.8090~~ $0.8125
Procysbi 75mg	$31.0500	$0.4140	~~6.08%~~ 6.10%	~~$0.0252~~ $0.0253	~~$0.0324~~ $0.0325	~~$2.4270~~ $2.4375
Cystagon 150mg	$1.1481	$0.0077	~~93.92%~~ 93.91%	$0.0072		

	Excess Revenues Market Share Approach (Germany excluded)[4]
Procysbi 25mg	~~$71,557.50~~ $71,531.25
Procysbi 75mg	~~$2,890,923.00~~ $2,889,862.50
TOTAL	~~$2,962,480.50~~ $2,961,393.75

(iii) Alternative 3: The Premium Comparison

54. In the further alternative, and to the extent that Horizon argues and this Board accepts that the enteric coating in Procysbi should justify *some* higher price for Procysbi over Cystagon, Board Staff submits that the introductory price of Procysbi was excessive because the relatively minor value of the enteric coating (and the consequent reduction in dosing schedule) cannot justify the extreme difference between the prices of Procysbi and Cystagon: the introductory international price of Procysbi is approximately 54 times greater than the price of

[4] Calculations of excess revenue are based, in part, on data from the filings of Horizon for 2017(2) and 2018(1).

Cystagon, as measured at the introduction of Procysbi. At best, under this alternative, a maximum non-excessive price for Procysbi that includes a premium for the value of the enteric coating should not be above the quarter-point between the price of Cystagon and the current price of Procysbi.

55. As a modified release formulation, Procysbi permits dosing every twelve (12) hours, rather than every six (6) hours, as is necessary for Cystagon. In order to recognize this possible secondary advantage, it is open to the Board to decide that a reasonable premium over the price of Cystagon *may* be warranted. The amount of the premium, however, should be proportionate to the minimal advantage of Procysbi over Cystagon.

56. To assist the Board in determining an appropriately proportionate price premium, reference may be had to general methodologies in the *Guidelines*. Although they are non-binding, they operationalize the statutory factors in section 85 of the Act, which the Board is legally required to consider. As such, the Guidelines represent one possible interpretation of the application of those legally-binding, statutory factors in some circumstances. However, it is important to recognize that the Guidelines are not the only possible interpretation of the factors, and ultimately, it is the factors (and not the Guidelines) that must prevail.

57. In this regard, the midpoint test that is set out in C.11.5 of the *Guidelines* provides an example of a methodology that results in a patentee being allowed to charge a higher price (or a premium) for a drug that provides moderate improvement.

58. However, the midpoint test in C.11.5 of the *Guidelines* originated in a situation where the price differential between the new drug and the comparators was relatively small. Where the differential in those prices is very large, as is the case here, the midpoint test can yield absurd results. In addition, Procysbi does not truly represent an improvement over Cystagon that justifies a 27-fold increase in price. Procysbi offers no clinical therapeutic advantage. Its only advantage is a reduction in the dosing schedule, which *may* result in increased compliance

rates. Moreover, while HDAP did assign Procysbi the category of "moderate improvement", HDAP acknowledged that this assignment was not based on clinical therapeutic improvement, and was merely based on "secondary factors" relating to the potential for increased patient compliance due to the reduction in the dosing schedule. The current scheme only provides for three categories of improvement and does not provide for a category between slight/no improvement and moderate improvement.

59. However, a *modified version* of the mid-point test may be an appropriate implementation of the s. 85(1) factors. On the one hand, it recognizes that Procysbi *may* have some minimal secondary benefit compared to Cystagon. On the other hand, it also takes into account (i) the very large difference between Cystagon's and Procysbi's prices; (ii) that CADTH, like the health agencies in many other countries, has recommended listing Procysbi only at a significantly reduced price; and (iii) that the Canadian and international prices of Procysbi may be artificial, given that these prices are set unilaterally by Horizon and yet have generated no meaningful sales, indicating that the list prices chosen by Horizon are not prices that the market will bear (i.e., purchasers are not buying Procysbi at its list prices, because they are excessive and do not reflect the true value of Procysbi). For these reasons, a modified version of the mid-point test (i.e., the Premium Comparison) would compare the price of Procysbi to the quarter point between the price of Procysbi and the TCC Test.

60. The application of the Premium Comparison results in Horizon having sold Procysbi at an excessive price calculated in accordance with the following table. The tables below calculates the TCC using the Canadian price for Cystagon and resulting excess revenues.

Drug	Top of the TCC (TCC) – using Canadian Cystagon Price	Median International Price (MIP) for Procysbi	Premium Comparison result (using Canadian Cystagon price)
Procysbi 25mg	$0.1913	$10.4462	$2.7550

Procysbi 75mg	$0.5740	$31.3382	$8.2651

Calculation of the Premium Test result: =0.25(MIP-TCC) + TCC

	Excess Revenues (Premium Comparison using Canadian Cystagon Price)[5]
Procysbi 25mg	$56,962.50
Procysbi 75mg	$2,301,274.90
TOTAL	**~~$2,577,926.25~~** **$2,358,237.40**

61. If the average of the PMPRB 7 prices for Cystagon are used, the results are similar and the application of the Premium Comparison results in Horizon having sold Procysbi at an excessive price. The tables for the prices and excess revenue are set out below:

Drug	Top of the TCC (TCC) – using average PMPRB 7 Cystagon Price	Median International Price (MIP) for Procysbi	Premium Comparison result (using average PMPRB7 Cystagon Price)
Procysbi 25mg	$0.4649	$10.4462	$2.9602
Procysbi 75mg	$1.3948	$31.3382	$8.8807

Calculation of the Premium Test result: =0.25(MIP-TCC) + TCC

	Excess Revenues (Premium Comparison using average PMPRB 7 Cystagon Price)[6]
Procysbi 25mg	$55,423.50
Procysbi 75mg	$2,239,099.30
TOTAL	$2,294,522.80

s. 85(2) of the *Act*

[5] Calculations of excess revenue are based, in part, on data from the filings of Horizon for 2017(2) and 2018(1).
[6] Calculations of excess revenue are based, in part, on data from the filings of Horizon for 2017(2) and 2018(1).

62. Board Staff submits that the factors set out in s. 85(1) of the Act are sufficient to support a conclusion that the price of Procysbi is excessive. However, in the alternative, Board Staff submits that the price of Procysbi is excessive under s. 85(2) and s 85(3) of the Act. These sections provide as follows:

> **(2)** Where, after taking into consideration the factors referred to in subsection (1), the Board is unable to determine whether the medicine is being or has been sold in any market in Canada at an excessive price, the Board may take into consideration the following factors:
>
> **(a)** the costs of making and marketing the medicine; and
>
> **(b)** such other factors as may be specified in any regulations made for the purposes of this subsection or as are, in the opinion of the Board, relevant in the circumstances.
>
> **(3)** In determining under section 83 whether a medicine is being or has been sold in any market in Canada at an excessive price, the Board shall not take into consideration research costs other than the Canadian portion of the world costs related to the research that led to the invention pertaining to that medicine or to the development and commercialization of that invention, calculated in proportion to the ratio of sales by the patentee in Canada of that medicine to total world sales.

63. Horizon has not incurred any eligible research and development costs in Canada.

64. The application of s. 85(2)(b) of the Act demonstrates that the price of Procysbi is excessive because it exceeds the price of other medicines that provide a similar dosing reduction as Procysbi vis-à-vis Cystagon: medicines where the same medicinal ingredient is available in an immediate and modified release with a less frequent dosing regimen.

65. The only difference between Procysbi and Cystagon is that Procysbi is a modified-release formulation, and Cystagon is not. A review of the Canadian publicly available prices of modified-release formulations which need to be administered less often than the immediate release formulations indicates that the modified release 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. On the other hand, Procysbi's price is approximately 54 times that of Cystagon in a regulatory environment where access to Cystagon is severely restricted as a result of the introduction of Procysbi. This indicates that Procysbi's price is out of the ordinary and excessive. Procysbi should not be priced at a level that is inconsistent with and above the generally observed differences between modified release medicines and their immediate release counterparts.

66. In a further alternative, should the Board consider that the facts set out in paras 2 to 31 above are not relevant to an analysis under s. 85(1) of the Act, Board Staff submits that they are relevant factors under s. 85(2)(b) of the Act.

Horizon Sells Procysbi at an Excessive Price and Order Required

67. Since 2017 and continuing to date, Horizon has been selling Procysbi in Canada at an excessive price.

68. Board Staff seeks the issuance of an Order pursuant to s. 83 of the *Act* as against Horizon, the terms of which are as follows:

(a) The price of Procysbi has been excessive since it was introduced in Canada on September 7, 2017.

(b) Horizon shall reduce the price of Procysbi within thirty (30) days of the Board's Order so that it is no higher than one of the following alternative amounts in accordance with one of the alternatives set out above and summarized below:

Description of Alternative	Procysbi 25mg/capsule	Procysbi 75mg/capsule
Same Medicine Comparison result using Canadian price for Cystagon	$0.1913	$0.5740

Same Medicine Comparison result using average PMPRB7 price for Cystagon	$0.4649	$1.3948
Market Share Comparison (including Germany)	$2.0475	$6.1425
Market Share Comparison (excluding Germany)	~~$0.8090~~ $0.8125	~~$2.4270~~ $2.4375
Premium Comparison result (using Canadian Cystagon price)	$2.7550	$8.2651
Premium Comparison result (using average PMPRB7 Cystagon Price)	$2.9602	$8.8807

(c) Horizon shall offset the excess revenue it has received from September 7, 2017 to the date of payment by making a payment in an amount to be calculated in accordance with the principles and tables set out in the Statement of Allegations. Excess revenues accrued up until December 31, 2018 are summarized below:[7]

Description of Alternative	Total
Same Medicine Comparison result using Canadian price for Cystagon	**$3,154,266.25**
Same Medicine Comparison result using average PMPRB7 price for Cystagon	**$3,069,313.45**
Market Share Comparison (including Germany)	**$2,577,926.25**
Market Share Comparison (excluding Germany)	~~**$2,962,480.50**~~ **$2,961,393.75**
Premium Comparison result (using Canadian Cystagon price)	~~**$2,577,926.25**~~ **$2,358,237.40**
Premium Comparison result (using average PMPRB7 Cystagon Price)	**$2,294,522.80**

(d) Horizon shall, within thirty (30) days of the Board's Order:

i. notify federal/provincial/territorial ministers of health, or their representatives, and all customers of the price decrease as

[7] Calculations of excess revenue are based, in part, on data from the filings of Horizon for 2017(2) and 2018(1).

required by the Board's Order (a copy of which shall be included in such notifications) and the effective date of such price decrease;

ii. submit copies of the above-noted notifications and any other notice to the Board; and

iii. provide to the Board information concerning the quantity of Procysbi sold and either the average price or the net revenue from sales of Procysbi in Canada, in the same form as required by subsection 4(1) of the *Regulations* for the period of September 7, 2017 to the date on which the price reduction referred to in paragraph c) comes into effect.

iv. Any other remedies Board Staff may seek and the Board may permit.

Perley-Robertson Hill & McDougall LLP
1400-340 Albert Street
Ottawa, Ontario K1R 0A5
Fax: (613) 238-8775

David Migicovsky
Tel: (613) 566-2833
Email: dmigicovsky@perlaw.ca

Christopher Morris
Tel: (613) 566-2802
Email: cmorris@perlaw.ca

Lawyers for Board Staff

LIST OF ATTACHMENTS

Attachment 1 – Product Monograph for Procysbi

Attachment 2 – Notice of Compliance for Procysbi, June 13, 2017

Attachment 3 – Canadian Patent No. CA2640531, “Enterically coated cysteamine, cystamine and derivatives thereof,” issued January 3, 2017 and pertaining to the medicine Cysteamine Bitartrate sold by the Respondent under the trade name Procysbi.

Attachment 4 – Canadian Patent No. CA2914770, “Delayed release cysteamine bead formulation, and methods of making and using same,” issued September 27, 2016 and pertaining to the medicine Cysteamine Bitartrate sold by the Respondent under the trade name Procysbi.