

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**

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 (CNDS)	0.0077 (CNDS)	0.0077 (CNDS)
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
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			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%	\$0.0756	\$0.0819	\$2.0475
Procysbi 75mg	\$31.0500	\$0.4140	18.25%	\$0.0756	\$0.0819	\$6.1425
Cystagon 150mg	\$1.1481	\$0.0077	81.75%	\$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

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

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

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%	\$0.0252	\$0.0324	\$0.8090
Procysbi 75mg	\$31.0500	\$0.4140	6.08%	\$0.0252	\$0.0324	\$2.4270
Cystagon 150mg	\$1.1481	\$0.0077	93.92%	\$0.0072		

	Excess Revenues Market Share Approach (Germany excluded) ⁴
Procysbi 25mg	\$71,557.50
Procysbi 75mg	\$2,890,923.00
TOTAL	\$2,962,480.50

(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 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

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

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: $=0.25(\text{MIP}-\text{TCC}) + \text{TCC}$

	Excess Revenues (Premium Comparison using Canadian Cystagon Price) ⁵
Procysbi 25mg	\$56,962.50

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

Procysbi 75mg	\$2,301,274.90
TOTAL	\$2,577,926.25

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: $=0.25(\text{MIP}-\text{TCC}) + \text{TCC}$

	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

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

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

(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	\$2.4270
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
Premium Comparison result (using Canadian Cystagon price)	\$2,577,926.25
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 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

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

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.

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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.

ATTACHMENT 1

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrPROCYSBI™

Cysteamine delayed-release capsules

25 mg and 75 mg cysteamine (as cysteamine bitartrate, also called mercaptamine bitartrate)

ATC code: A16AA04
Amino Acids and Derivatives

Horizon Pharma Ireland Ltd.
Connaught House, 1st Floor
1 Burlington Road
Dublin 4, D04 C5Y6
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Date of Preparation:
June 08, 2017

Imported and distributed by:
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PROCYSBI™

Cysteamine delayed-release capsules
(as cysteamine bitartrate, also called mercaptamine bitartrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Delayed-release capsules, 25 mg and 75 mg cysteamine (as cysteamine bitartrate)	Methacrylic acid copolymer <i>For a complete listing of ingredients see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

PROCYSBI (cysteamine delayed-release capsules) is indicated for the treatment of nephropathic cystinosis.

PROCYSBI treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.

Pediatrics (< 18 years):

The safety and efficacy of PROCYSBI in patients under 2 years of age have not been established. See WARNINGS AND PRECAUTIONS, Special Populations and CLINICAL TRIALS.

Geriatrics (≥ 65 years of age):

The safety and efficacy of PROCYSBI in patients 65 years and older with cystinosis have not been established. See WARNINGS AND PRECAUTIONS, Special Populations and CLINICAL TRIALS.

CONTRAINDICATIONS

PROCYSBI is contraindicated for use in patients:

- who are hypersensitive to cysteamine bitartrate, any form of cysteamine or to any ingredient in the formulation, including non-medicinal ingredients, or to any component of the container. For a complete listing of ingredients, see the Dosage Forms, Composition and Packaging section of the product monograph.
- who are hypersensitive to penicillamine.

WARNINGS AND PRECAUTIONS

General

Ehlers-Danlos-like Syndrome: Skin and bone lesions that resemble clinical features of Ehlers-Danlos syndrome have been reported in patients treated with high doses of immediate-release cysteamine bitartrate or other cysteamine salts. These include purplish hemorrhagic lesions (which have been described as molluscoid pseudotumors), skin striae, bone lesions (including osteopenia, compression fractures, scoliosis and genu valgum), leg pain and joint hyperextension. One patient on immediate-release cysteamine bitartrate with serious skin lesions subsequently died of acute cerebral ischemia with marked vasculopathy. Monitor patients for development of skin or bone lesions and interrupt PROCYSBI dosing if patients develop these lesions. PROCYSBI may be restarted at a lower dose under close supervision, then slowly increased to the appropriate therapeutic dose.

Gastrointestinal

Gastrointestinal (GI) ulceration and bleeding have been reported in patients receiving immediate-release cysteamine bitartrate. GI tract symptoms including nausea, vomiting, anorexia and abdominal pain, sometimes severe, have been associated with PROCYSBI.

Physicians should remain alert for signs of ulceration and bleeding and should inform patients and/or guardians about the signs and symptoms of serious GI toxicity and what steps to take if they occur. If severe GI tract symptoms develop, consider decreasing the dose of PROCYSBI.

Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) was first described in cystic fibrosis patients who were given high doses of pancreatic enzymes in the form of tablets with an enteric coating of methacrylic acid-ethyl acrylate copolymer, one of the excipients in PROCYSBI. As a precaution, unusual abdominal symptoms or changes in abdominal symptoms should be medically assessed to exclude the possibility of fibrosing colonopathy.

Hepatic

PROCYSBI has not been studied in patients with hepatic impairment. Closer monitoring of the WBC cystine levels is recommended in these patients.

Monitoring and Laboratory Tests:

White blood cell (WBC) cystine levels

WBC cystine levels should be routinely monitored to assess the effect of PROCYSBI treatment on intracellular cystine depletion.

Refer to the assay-specific therapeutic target for cystine depletion provided by individual testing laboratories. The target WBC cystine concentration measured using the traditional mixed leukocyte assay is less than 1.0 nmol ½ cystine/mg protein. Assays using specific WBC subsets (e.g. granulocyte method) have different treatment targets.

Obtain blood samples for WBC cystine concentration measurement at drug trough (as close to 30 minutes post dosing as possible). See DOSAGE AND ADMINISTRATION. In addition, it is important to accurately record the time of the last dose, the actual dose consumed, and the time the blood sample was taken.

The recommended frequency of monitoring WBC cystine concentration is as follows:

- For cysteamine-naïve patients: Obtain measurement every two to four weeks while titrating the dose of PROCYSBI until reaching the maintenance PROCYSBI dose (see Table 4, DOSAGE AND ADMINISTRATION for maintenance doses), then monthly for 3 months, quarterly for 1 year, and twice-yearly thereafter, at a minimum.
- For patients switching from immediate-release cysteamine to PROCYSBI: Obtain measurement every two weeks while titrating the dose of PROCYSBI, quarterly for 6 months, and twice yearly thereafter, at a minimum.

More frequent monitoring of WBC cystine concentration is recommended when drugs that increase the gastric pH are introduced and when dose adjustments occur. See DRUG INTERACTIONS.

Because the measured WBC cystine concentration depends on the assays used for cystine and total protein content, individual patient sample concentration values from different assays and laboratories may not be interchangeable. Consideration of assay results must be made with knowledge of the specific assays used. Therefore, communication should be maintained with the laboratory performing the assay.

Leukopenia

Cysteamine, as an immediate-release formulation, has been associated with reversible leukopenia levels. Monitor WBC counts. If WBC levels remain abnormally decreased, consider decreasing the dose or discontinuing PROCYSBI until values revert to normal.

Alkaline Phosphatase

Cysteamine, as an immediate-release formulation, has been associated with elevated alkaline phosphatase levels. Monitor alkaline phosphate levels. If values remain elevated, consider decreasing the dose or discontinuing PROCYSBI until values revert to normal.

Neurologic

Central nervous system (CNS) symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with immediate-release cysteamine bitartrate. Carefully evaluate and monitor patients who develop CNS symptoms. Interrupt medication or adjust the dose as necessary for patients with severe symptoms or with symptoms that persist or progress.

Benign intracranial hypertension (pseudotumor cerebri; PTC) and/or papilledema have been reported in patients receiving immediate-release cysteamine bitartrate treatment. Physicians

should monitor patients for signs and symptoms of PTC, including headache, tinnitus, dizziness, nausea, diplopia, blurry vision, loss of vision, pain behind the eye or pain with eye movement. If signs/symptoms persist, interrupt dosing or decrease the dose and refer the patient to an ophthalmologist. If the diagnosis is confirmed, permanently discontinue use of PROCYSBI.

Ophthalmologic

Oral cysteamine has not been shown to prevent eye deposition of cystine crystals. Therefore, where cysteamine ophthalmic solution is used for that purpose, its use should continue.

Renal

The effect of severe renal impairment and end stage renal disease on the pharmacokinetics of PROCYSBI have not been evaluated. See ACTION AND CLINICAL PHARMACOLOGY, Special Populations.

Some forms of cysteamine are less well tolerated (i.e. leading to more adverse events) when patients are on dialysis. Closer monitoring of the WBC cystine levels is recommended in patients with severe or end stage renal disease.

Skin

Serious skin rashes such as erythema multiforme bullosa, Stevens-Johnson Syndrome (SJS), or toxic epidermal necrolysis have been reported in patients receiving immediate-release cysteamine bitartrate. If serious skin rashes develop, permanently discontinue use of PROCYSBI.

Special Populations

Pregnant Women:

There are no available data on PROCYSBI use in pregnant women. Cysteamine (administered as cysteamine bitartrate) was teratogenic and fetotoxic in rats at doses less than the recommended human maintenance dose. See TOXICOLOGY.

Before starting PROCYSBI in a woman of child-bearing potential, pregnancy status should be confirmed.

Patients should be advised of the potential risk to a fetus and the importance of ensuring adequate contraception while taking PROCYSBI. Women who become pregnant or are planning to become pregnant should be instructed to immediately contact their physician. In the event of pregnancy, interruption of treatment with PROCYSBI should be considered or appropriate medical care instituted.

Breastfeeding:

There is no information on the presence of cysteamine in human milk, or its effects on the breast-fed infant. Cysteamine is present in the milk of lactating rats. Growth retardation and a decrease

in survival occurred in neonatal rats nursed by mothers receiving cysteamine. See TOXICOLOGY, Reproductive Toxicology.

Because of the potential for serious adverse reactions in breastfed infants from cysteamine, breastfeeding is not recommended.

Pediatrics (< 18 years of age):

There are no data in children < 2 years of age from clinical trials of PROCYSBI. See CLINICAL TRIALS.

Geriatrics (≥ 65 years of age):

The safety and efficacy of PROCYSBI in patients aged 65 years and older have not been established.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse drug reactions (ADRs) reported most frequently (≥5%) for PROCYSBI in a short-term trial (Study 03) included nausea, vomiting (11.6% each), and abdominal pain (7.0%).

ADRs reported most frequently with long-term treatment with PROCYSBI (Study 04) included vomiting (33.9%), nausea (15.3%), abdominal pain (13.6%), breath odour (13.6%), diarrhea (8.5%), and skin odour abnormal (8.5%).

In Study 03, one serious adverse event (SAE), abdominal discomfort in a patient receiving treatment with PROCYSBI, was considered drug-related. In Study 04, six SAEs were assessed as drug-related: renal failure, constipation, vomiting (two SAEs), diarrhea and acute gastroenteritis.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Sixty-two patients with cystinosis (38 males and 24 females) received PROCYSBI in two clinical trials (Studies 03 and 04) at doses ranging from 0.29 grams/m² per day to 2.19 grams/m² per day. All patients were transitioned from immediate-release cysteamine bitartrate to PROCYSBI. Forty-three patients, aged 7 to 24 years, received PROCYSBI in an 9-week, open-label, randomized sequence, cross-over trial comparing 3 weeks of treatment with PROCYSBI to 3 weeks of treatment with immediate-release cysteamine bitartrate (Study 03). Forty of 43 patients continued PROCYSBI treatment in an open-label, uncontrolled extension trial, and were treated with PROCYSBI for an average of 3 years (Study 04). An additional 19 patients (6

patients with a renal transplant, and 13 patients aged 2 to 6 years) were enrolled directly into this trial and were treated with PROCYSBI.

Overall, 14 patients (32.6%) in Study 03 experienced one or more treatment-emergent adverse events (TEAEs) that were assessed as treatment-related. ADRs reported with a frequency of $\geq 1\%$ are shown in Table 1.

In the long-term extension trial, Study 04, 35 patients (59%) experienced one or more TEAEs which were assessed as treatment-related. ADRs reported with a frequency of $\geq 1\%$ are shown in Table 2. ADRs are consistent with those reported in Study 03 and with those previously described for immediate-release cysteamine bitartrate. ADRs within the subpopulations of patients ≤ 6 years of age (n=13) and in the renal transplant recipients (n=6) suggest a similar safety profile to that observed in patients from Study 03 (n=40).

Abnormal Hematologic and Clinical Chemistry Findings

There were no changes observed in laboratory tests results for PROCYSBI during the clinical trials beyond that expected with nephropathic cystinosis.

Post-Market Adverse Drug Reactions

As post-market reports of adverse reactions are reported voluntarily from a population of uncertain size and demographics, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Post-marketing experience with PROCYSBI

In cumulative post-market data for PROCYSBI reported from the United States (US) and the European Union (EU), the most frequently reported serious adverse events include renal disorders (such as interstitial nephritis, renal transplant, kidney transplant rejection, renal failure, and dialysis) and dehydration.

Post-marketing experience with immediate-release cysteamine

The following adverse reactions have been identified during post-market approval of immediate release cysteamine: Musculoskeletal (joint hyperextension, leg pain, osteopenia, compression fracture, scoliosis, genu valgum); Skin (erythema multiforme bullosa, toxic epidermal necrolysis, Ehlers-Danlos-like syndrome, molluscoid pseudotumours, skin striae, skin fragility); Central Nervous System (seizures, lethargy, somnolence, depression, and encephalopathy, benign intracranial hypertension and/or papilledema); and Renal (nephrotic syndrome, due to membranous glomerulonephritis of renal allograft in one case, hypersensitivity interstitial nephritis in another).

See WARNINGS AND PRECAUTIONS.

Table 1: Adverse Reactions^a that Occurred in One or More Patients in the Randomized, Crossover Clinical Trial (Study 03)

MedDRA System Organ Class Preferred Term	PROCYSBI n= 43 n (%)	Immediate-Release Cysteamine Bitartrate n= 41 n (%)
Cardiac disorders		
Atrioventricular block	0 (0)	1 (2.4)
Gastrointestinal disorders^b		
Vomiting	5 (11.6)	3 (7.3)
Nausea	5 (11.6)	2 (4.9)
Abdominal pain	3 (7.0)	0 (0)
Abdominal discomfort	1 (2.3)	0 (0)
Diarrhoea	1 (2.3)	1 (2.4)
General disorders and administration site conditions		
Malaise	1 (2.3)	0 (0)
Metabolism and nutrition disorders		
Decreased appetite	1 (2.3)	1 (2.4)
Nervous system disorders		
Dizziness	1 (2.3)	0 (0)
Headache	1 (2.3)	0 (0)
Renal and urinary disorders		
Renal impairment	2 (4.7)	0 (0)
Skin and subcutaneous tissue disorders		
Cold sweat	1 (2.3)	0 (0)
Vascular disorders		
Flushing	1 (2.3)	0 (0)

Note: A patient is counted once if he/she reported one or more events. Percentages are based on the number of patients in the safety population within each treatment group. Coded using MedDRA, Version 13.0.

^a Defined as treatment emergent adverse events that have been assessed by the study Investigator to be possibly or probably related to study treatment.

^b Use of gastric acid reducing medications, including proton pump inhibitors, was allowed during treatment with immediate-release cysteamine bitartrate but restricted to intolerable gastric upset during RP103 treatment.

Table 2: Adverse Reactions^a that Occurred in One or More Patients while Receiving PROCYSBI in a Long-Term Clinical Trial

(Study 04)

MedDRA System Organ Class Preferred Term	Overall (N=59) N (%)
Blood and lymphatic system disorders	
Neutropenia	1 (1.7%)
Pancytopenia	1 (1.7%)
Gastrointestinal disorders	
Vomiting	20 (33.9%)
Nausea	9 (15.3%)
Abdominal pain	8 (13.6%)
Breath odour	8 (13.6%)
Diarrhea	5 (8.5%)
Abdominal pain upper	2 (3.4%)
Constipation	1 (1.7%)
Dyspepsia	1 (1.7%)
Dysphagia	1 (1.7%)
Flatulence	1 (1.7%)
Gastroesophageal reflux disease	1 (1.7%)
Peptic ulcer	1 (1.7%)
General disorders and administration site conditions	
Device occlusion	2 (3.4%)
Fatigue	2 (3.4%)
Pain	1 (1.7%)
Infections and infestations	
Gastroenteritis	1 (1.7%)
Nasopharyngitis	1 (1.7%)
Metabolism and nutrition disorders	
Decreased appetite	3 (5.1%)
Nervous system disorders	
Headache	2 (3.4%)
Renal and urinary disorders	
Renal failure	1 (1.7%)
Skin and subcutaneous tissue disorders	
Skin odour abnormal	5 (8.5%)
Alopecia areata	1 (1.7%)
Skin hypopigmentation	1 (1.7%)
Vascular disorders	
Hot flush	1 (1.7%)

Note: A patient is counted once if he/she reported one or more events. Coded using MedDRA, Version 13.0.

^a Defined as treatment emergent adverse events that have been assessed by the study Investigator to be possibly or probably related to the use of PROCYSBI.

DRUG INTERACTIONS

Overview

There is some potential for drug interaction based on the induction of CYP1A2 and CYP3A4 (and possibly CYP2B6) by cysteamine bitartrate based on *in vitro* data.

When drugs that increase the gastric pH are introduced, more frequent monitoring of WBC cystine concentration is recommended. Dose adjustment of PROCYSBI may be required when taken with these drugs.

Bicarbonate or carbonate should be administered at least one hour before or one hour after PROCYSBI.

Other than bicarbonate/carbonate (see above), PROCYSBI can be co-administered with electrolytes and mineral replacements necessary for management of Fanconi Syndrome, as well as vitamin D and thyroid hormone. See DOSAGE AND ADMINISTRATION, Administration.

Alcohol should be avoided while taking PROCYSBI.

Drug-Drug Interactions

Drugs that Increase Gastric pH

Drugs that increase the gastric pH (e.g. proton pump inhibitors, medications containing bicarbonate or carbonate) may cause premature release of cysteamine from PROCYSBI, and thus increase WBC cystine concentration. Therefore, more frequent monitoring of WBC cystine concentration is recommended when drugs that increase the gastric pH are introduced. See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests. Dose adjustment of PROCYSBI may be required if taken with these drugs.

Bicarbonate or carbonate should be administered at least one hour before or one hour after PROCYSBI to avoid potential earlier release of cysteamine. See DOSAGE AND ADMINISTRATION.

Concomitant administration of 20 mg, multiple dose omeprazole did not significantly affect the pharmacokinetics of cysteamine when PROCYSBI was administered with 240 mL of orange juice. The effect of omeprazole on the pharmacokinetics of cysteamine was not studied after PROCYSBI administration with water. More frequent monitoring of WBC cystine concentration is recommended with omeprazole as with all other drugs that increase gastric pH.

See DETAILED PHARMACOLOGY, *In Vitro* Drug Interaction Studies, for additional information regarding other studies.

Drug-Food Interactions

Interactions with foods have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Avoid drinking alcohol while taking PROCYSBI. Consumption of alcohol with PROCYSBI may increase the rate of cysteamine release and/or adversely alter effectiveness and safety of PROCYSBI.

Patients should exercise caution when driving or engaging in other hazardous activities when taking cysteamine. Cysteamine may cause drowsiness. See WARNINGS AND PRECAUTIONS, Neurologic.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Treatment with PROCYSBI should be started immediately after diagnosis of nephropathic cystinosis.

The PROCYSBI dosing regimen is different for cysteamine-naïve patients and patients switching from immediate-release cysteamine.

Titration of PROCYSBI dose is performed based on the assessment of WBC cystine concentrations, as well as drug tolerability. See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

Do not exceed 1.95 grams/m² per day due to an increased incidence of adverse reactions. See WARNINGS AND PRECAUTIONS.

If PROCYSBI is taken with drugs that increase gastric pH, such as proton pump inhibitors and bicarbonate, more frequent monitoring of WBC cystine levels is recommended and dose adjustment of PROCYSBI may be required. See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and DRUG INTERACTIONS.

Recommended Dose and Dosage Adjustment

PROCYSBI is available as a capsule in 25 mg and 75 mg strengths. Directions for starting and maintenance dosages and methods of administration are presented below.

Switching Patients from Immediate-Release Cysteamine

When switching patients from immediate-release cysteamine to PROCYSBI, the recommended starting total daily dose of PROCYSBI is equivalent to their previous total daily dose of immediate-release cysteamine.

For individuals for whom GI tolerability is a known concern, initiation of PROCYSBI at 75% of the immediate-release cysteamine dose may be considered. However, this may reduce the effectiveness of PROCYSBI; therefore, WBC cystine levels should be monitored more closely. See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and CLINICAL TRIALS.

Measure WBC cystine concentration every two weeks while titrating the dose of PROCYSBI, then quarterly for one year, and twice yearly thereafter at a minimum. Titrate the PROCYSBI dose as needed to achieve target WBC cystine concentrations.

Do not exceed 1.95 g/m² per day. See Dose Titration.

Starting Dose in Cysteamine-Naïve Patients

The recommended starting dosage of PROCYSBI for cysteamine-naïve patients is 0.2 to 0.3 grams/m² per day divided into two doses given every 12 hours.

Table 3 shows the recommended weight-based starting dosage and the number of capsules needed to achieve each dose. Increase the dosage gradually over 4 to 6 weeks until the maintenance dosage is achieved to help reduce the risk of adverse reactions.

Maintenance Dose in Cysteamine-Naïve Patients

The usual recommended maintenance dose of PROCYSBI for cysteamine-naïve patients is 1.30 grams/m² per day, divided into two equal doses given every 12 hours.

Table 4 shows the recommended weight-based maintenance dosage of PROCYSBI and the number of capsules needed to achieve each dose. After the target maintenance dose has been achieved, measure the WBC cystine concentration monthly for 3 months, then quarterly for one year, and twice yearly thereafter at a minimum. Titrate the PROCYSBI dosage as needed to maintain target WBC cystine concentrations. See Dose Titration. Do not exceed 1.95 grams/m² per day.

Table 3: Recommended Weight-Based Starting Dosage ($\frac{1}{6}$ to $\frac{1}{4}$ of maintenance dosage)

	Target Maintenance Dosage	Starting Dosage as a Fraction of the Target Maintenance Dosage			
Weight in kilograms	PROCYSBI dosage in mg every 12 hours	Number of capsules every 12 hours			
		$\frac{1}{6}$ of target		$\frac{1}{4}$ of target	
		75mg	25mg	75mg	25mg
0-5	200	0	1	0	2
6-10	300	0	2	1	0
11-15	400	1	0	1	1
16-20	500	1	1	1	2
21-25	600	1	1	2	0
26-30	700	1	2	2	1
31-40	800	1	2	2	2
41-50	900	2	0	3	0
	1000	2	1	3	1
51 and greater	> 1000 ^a	Calculate number of capsules required for the prescribed dose			

^a Do not exceed 1.95 grams/m² per day.

Table 4: Target Weight-Based Maintenance Dosage

Weight in Kilograms	PROCYSBI Maintenance Dosage in mg every 12 hours	Number of capsules every 12 hours	
		75 mg	25 mg
0 – 5	200	2	2
6-10	300	4	0
11-15	400	5	1
16-20	500	6	2
21-25	600	8	0
26-30	700	9	1
31-40	800	10	2
41-50	900	12	0
	1000	13	1
51 and greater	> 1000 ^a	Calculate number of capsules required for the prescribed dose	

^a Do not exceed 1.95 grams/m² per day.

Dose Titration

- Adjust the dose of PROCYSBI to produce target WBC cystine levels. If the WBC cystine concentration is greater than the target level (See WARNINGS AND PRECAUTIONS, Monitoring And Laboratory Tests, WBC Cystine levels), consider the following before dose adjustment: adherence to medication and dosing interval, the

timing between the last dose and the blood draw for the laboratory measurement, and the timing of PROCYSBI administration in relation to food or other administration instructions.

- Measurement timing: WBC cystine levels should be obtained 12.5 hours after the evening dose and therefore 30 minutes following morning dose (i.e. at drug trough). See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, WBC Cystine levels. If a dose adjustment is required, increase the dose by 10%.
- **Do not exceed a maximum dose of 1.95 grams/m² per day due to an increased risk of adverse reactions.**
- If adverse reactions occur, decrease the PROCYSBI dose. For patients who have initial intolerance, temporarily discontinue PROCYSBI and then re-start at a lower dose and gradually increase to the target dose.
- Some patients may be unable to achieve their therapeutic target due to poor tolerability of PROCYSBI. Patients with poor tolerability still receive benefit if white blood cell cystine levels are below 2 nmol ½ cystine/mg protein.

Missed Dose

Patients should be instructed that if a dose is missed, it should be taken as soon as possible up to 8 hours after the scheduled time. However, if a dose is missed and the next scheduled dose is due in less than 4 hours, the patient should be instructed not to take the missed dose, and to take the next dose at the usual scheduled time. Patients should be instructed not to take 2 doses at the same time to make up for a missed dose.

Administration

Food should not be eaten for at least 2 hours before or 2 hours after taking PROCYSBI to maximize absorption. If this is not possible, food can be taken 30 minutes after PROCYSBI. Take PROCYSBI in a consistent manner in regard to food. Avoid food high in fat or proteins (e.g. dairy) close to dosing of PROCYSBI.

PROCYSBI capsules should be swallowed whole with orange juice. Patients should not crush or chew capsules or capsule contents.

Avoid drinking alcohol while taking PROCYSBI (see Drug-Lifestyle Interactions).

Administer PROCYSBI at least 1 hour before, or 1 hour after, medications containing bicarbonate or carbonate (see DRUG INTERACTIONS).

In pediatric patients who are at risk of aspiration, aged approximately 6 years and under, the hard capsules should be opened and the content sprinkled on applesauce.

For patients who have difficulty swallowing capsules, follow the instructions below for administration with applesauce.

Administration with Applesauce:

1. Place approximately 4 ounces (1/2 cup) of either applesauce into a clean container
2. Open the capsule(s)
3. Sprinkle the intact granules on applesauce
4. Mix the granules with the applesauce
5. Consume the entire contents within 30 minutes of mixing. Do not chew the granules. Do not save the applesauce and granules for later use.

Administration with Applesauce via a Gastrostomy Tube (G-Tube) 14 French or larger:

A bolus (straight) feeding tube is recommended.

1. Flush the gastrostomy tube button first with 5 mL of water to clear the button
2. Open the capsule and empty the granules into a clean container with approximately 4 ounces (1/2 cup) of applesauce. Use only strained applesauce with no chunks. A minimum of 1 ounce (1/8 cup) of applesauce may be used for children ≤ 25 kg starting PROCYSBI at a dose of 1 or 2 capsules.
3. Mix the intact granules into the applesauce.
4. Draw up the mixture into a syringe. Keep the feeding tube horizontal during administration and apply rapid and steady pressure (10 mL/10 seconds) to dispense the syringe contents into the tube within 30 minutes of preparation.
5. Repeat step 3 until all of the mixture is administered. Do not save the applesauce and granule mixture for later use.
6. Draw up a minimum of 10 mL of orange juice into another syringe, swirl gently, and flush the tube.

Administration of PROCYSBI with foods and liquids not included above or by other methods has not been studied clinically.

OVERDOSAGE

Nausea, vomiting, abdominal discomfort, and dehydration have been reported following overdosage; the symptoms resolved with supportive care.

An overdose of cysteamine may cause progressive lethargy.

Should overdosing occur, adequate respiratory and cardiovascular systems support should be provided. There is no known antidote for cysteamine. Hemodialysis may be considered since cysteamine is poorly bound to plasma proteins.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Cysteamine is an aminothiols that participates in a thiol-disulfide interchange reaction within lysosomes, converting cystine into cysteine and cysteine-cysteamine mixed disulfide, both of which can exit the lysosome in patients with cystinosis.

Pharmacodynamics

Using the mixed leukocyte assay, normal individuals and persons heterozygous for cystinosis have WBC cystine levels of less than 0.2 and usually below 1 nmol $\frac{1}{2}$ cystine/mg protein, respectively. Untreated patients with nephropathic cystinosis have elevations of WBC cystine concentration above 2 nmol $\frac{1}{2}$ cystine/mg protein.

After the administration of a single dose of PROCYSBI, peak concentrations of WBC cystine were observed at 3 hours post-dose. The nadir of WBC cystine closely followed the peak concentrations at 3.5 hours post-dose, and returned to baseline WBC concentrations at 12 hours post dose.

In the open-label, randomized, cross-over trial, PROCYSBI administered every twelve hours maintained WBC cystine levels < 1 nmol $\frac{1}{2}$ cystine/mg protein in patients who were previously receiving immediate-release cysteamine bitartrate administered every six hours. In the long-term extension study, 40 out of 41 patients continued treatment with PROCYSBI for approximately 36 months and maintained WBC cystine control below 1 nmol $\frac{1}{2}$ cystine/mg protein for the study duration. See CLINICAL TRIALS.

Pharmacokinetics

The pharmacokinetics of PROCYSBI were evaluated in 43 patients with cystinosis and with an estimated glomerular filtration rate of > 30 mL/minutes/1.73m² (Study 03).

Table 5 shows the mean (\pm SD) pharmacokinetic parameters for PROCYSBI and immediate-release cysteamine bitartrate after one dose at steady state. The mean C_{\max} and AUC_{\inf} were 3.6 mg/L and 726 min*mg/L for PROCYSBI and 2.7 mg/L and 380 min*mg/L for immediate-release cysteamine bitartrate.

Table 5: Pharmacokinetic parameters for cysteamine after a single dose of PROCYSBI or immediate-release cysteamine bitartrate at steady state (Study 03)

	Immediate-release cysteamine bitartrate Mean \pm SD	PROCYSBI
C_{\max} (mg/L)	2.7 \pm 1.4	3.6 \pm 1.8
AUC _{0-6h} (min*mg/L)	351 \pm 153	NA
AUC _{0-12h} (min*mg/L)	NA	726 \pm 339
AUC _{inf} (min*mg/L)	380 \pm 157	785 \pm 358
T _{max} (min)	73 \pm 31	188 \pm 88
t _{1/2} (min)	90 \pm 24	253 \pm 403
Cl/F (L/min)	1.4 \pm 0.8	1.2 \pm 0.8
Vd/F (L)	198 \pm 159	382 \pm 404

Absorption:

The pharmacokinetics of PROCYSBI are consistent with those of a delayed-release formulation; the mean T_{max} for PROCYSBI was 188 minutes compared with 73 minutes for immediate-release cysteamine bitartrate. The systemic exposure to cysteamine was similar when PROCYSBI was administered with orange juice as a whole capsule and sprinkled in applesauce in the fasted state. In a food effect study conducted in healthy subjects (n=20), administration of a meal 30 minutes following PROCYSBI administration (intact capsules), decreased C_{max} by 34% and AUC_{0-t} by 32% compared to administration of a meal 2 hours post dose (see DOSAGE AND ADMINISTRATION).

Food intake two hours after administration did not affect the absorption of PROCYSBI.

Distribution:

Cysteamine was moderately bound to human plasma proteins, predominantly to albumin, with mean protein binding of about 52%. Plasma protein binding was independent of concentration over the concentration range achieved clinically with the recommended doses. The volume of distribution (Vd/F) was 382 L for PROCYSBI compared with 198 L for immediate-release cysteamine bitartrate.

Metabolism:

In vitro data suggests that cysteamine bitartrate is likely to be metabolized by multiple CYP enzymes, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. CYP2A6 and CYP3A4 were not involved in the metabolism of cysteamine bitartrate under the experimental conditions.

Excretion:

After each dose of PROCYSBI the cysteamine concentration in the blood continues to decline for approximately 30 minutes and the WBC cystine concentration increases accordingly.

The apparent plasma clearance (Cl/F) was similar between PROCYSBI (1.2 L/min) and immediate-release cysteamine bitartrate (1.4 L/min). The terminal half-life ($t_{1/2}$) was 253 minutes for PROCYSBI and 90 minutes for immediate-release cysteamine bitartrate.

The elimination of unchanged cysteamine in the urine has been shown to range between 0.3 % and 1.7% of the total daily dose in four patients; the bulk of cysteamine is excreted as sulphate.

Special Populations and Conditions

Pediatrics (< 18 years):

The safety and efficacy of PROCYSBI in patients under 2 years of age have not been established. See INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS, Special Populations, and CLINICAL TRIALS.

Geriatrics (≥ 65 years of age):

The safety and efficacy of PROCYSBI in patients 65 years and older with cystinosis have not been established. See INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS, Special Populations, and CLINICAL TRIALS.

Gender:

The influence of gender on the pharmacokinetics of PROCYSBI has not been studied.

Race:

The influence of race on the pharmacokinetics of PROCYSBI has not been studied.

Hepatic Insufficiency:

PROCYSBI has not been studied in patients with hepatic impairment.

Renal Insufficiency:

The effect of severe renal impairment and end stage renal disease on the pharmacokinetics of PROCYSBI have not been evaluated. Closer monitoring of WBC cystine levels is recommended in these patients. See WARNINGS AND PRECAUTIONS, Renal.

Genetic Polymorphism:

The influence of genetic polymorphism on the pharmacokinetics of PROCYSBI has not been studied.

STORAGE AND STABILITY

PHARMACIST: Prior to Dispensing: Store in a refrigerator, 2 °C to 8 °C (36 °F to 46 °F).

PATIENT: Store at room temperature, 20 °C to 25 °C (68 °F to 77 °F).

Do not remove desiccant or oxygen absorber(s) from the container. Keep bottles tightly closed and store away from light and moisture.

SPECIAL HANDLING INSTRUCTIONS FOR THE PHARMACIST

Dispense PROCYSBI with a 3 month expiration date.

Specify “Store at room temperature, 20 °C to 25 °C (68 °F to 77 °F).”

Dispense only in original packaging. Do not subdivide or repackage.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PROCYSBI (cysteamine delayed-release capsules) is available in 25 mg and 75 mg strengths.

25 mg Delayed-Release Capsules:

Each 25 mg capsule contains 73.7 mg cysteamine bitartrate, equivalent to 25 mg cysteamine in a size 3 capsule. The capsules have a light blue opaque cap imprinted with the Raptor logo in white ink and a light blue opaque body imprinted with “25 mg” in white ink.

PROCYSBI 25 mg delayed-release capsules are supplied in white high density polyethylene (HDPE) bottles with child-resistant closures containing 60 capsules per bottle. Each bottle includes one oxygen absorber canister and one desiccant canister.

75 mg Delayed-Release Capsules:

Each 75 mg delayed-release capsule contains 221.1 mg cysteamine bitartrate, equivalent to 75 mg cysteamine in a size 0 capsule. The capsules have a dark blue opaque cap imprinted with the ‘Raptor’ logo in white ink and light blue opaque body imprinted with ‘75 mg’ in white ink.

PROCYSBI 75 mg delayed-release capsules are supplied in white high density polyethylene (HDPE) bottles with child-resistant closures containing 250 capsules per bottle. Each bottle includes two oxygen absorber canisters and one desiccant canister.

PROCYSBI 25 mg and 75 mg capsules contain the following inactive ingredients:

Capsule Contents: Hypromellose, methacrylic acid copolymer, microcrystalline cellulose, purified water, sodium lauryl sulfate, talc and triethyl citrate.

Capsule Shell Ingredients: FD&C Blue#2, gelatin and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Cysteamine Bitartrate (also called mercaptamine bitartrate)

Chemical name: Ethanethiol, 2-amino,[R-(R*,R*)]-2,3-dihydroxybutanedioate(1:1) salt, or
Mercaptamine Bitartrate (INN), or
2-Aminoethanethiol Bitartrate

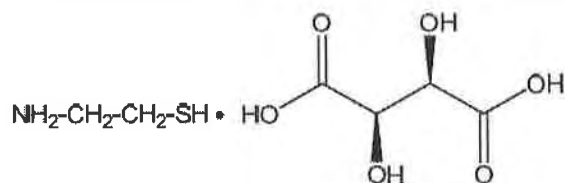
Molecular formula:

Cysteamine (free base): C_2H_7NS
Cysteamine bitartrate: $C_2H_7NS \cdot C_4H_6O_6$

Molecular mass:

Cysteamine (free base): 77.15 Da
Cysteamine bitartrate: 227.24 Da

Structural formula:



Physicochemical properties:

Description: White crystalline powder
Polymorphism: Form A (monohydrate form); Form B (anhydrous form)
Solubility: Cysteamine bitartrate is freely soluble in water (>100 mg/mL), and is freely soluble in aqueous media across pH 1.2 to 7.2
Melting range: 118 - 121°C
Acid pKa: 8.19
Basic pKa: 10.61

Table 6: Solubility of Cysteamine Bitartrate

pH condition	Cysteamine bitartrate concentration (mg/mL), Mean \pm SD, n=3
1.2 (hydrochloric acid/potassium chloride buffer, 50 mM)	158.9 \pm 8.9
3.0 (potassium phosphate buffer, 50 mM)	109.1 \pm 0.6
4.5 (sodium acetate buffer, 50 mM)	166.6 \pm 13.2
6.8 (potassium phosphate buffer, 50 mM)	216.6 \pm 3.3
7.2 (potassium phosphate buffer, 50 mM)	222.4 \pm 1.3

CLINICAL TRIALS

The two clinical trials that support the efficacy and safety of PROCYSBI for the treatment of nephropathic cystinosis are listed in Table 7. Study 03 was an open-label, randomized, active-controlled, 9-week crossover study that compared the safety, efficacy, tolerability, pharmacokinetics, and pharmacodynamics of PROCYSBI administered every 12 hours (Q12H) to immediate-release cysteamine bitartrate administered every 6 hours (Q6H) in patients with cystinosis. Study 04 is a long-term, open-label extension study of RP103 in cystinosis subjects. The maximum treatment duration with PROCYSBI in Study 04 is approximately 4.6 years.

Table 7: Summary of Patient Demographics for Study 03 and 04 conducted with PROCYSBI in patients with Nephropathic Cystinosis

Study #	Trial design	Dosage, route of administration and duration	No of Study Patients Enrolled	Mean age (Range)	Sex (%)
Study 03	Open-label, multicenter, randomized crossover	PROCYSBI 25 mg and 75 mg capsules Q12H vs. immediate-release cysteamine bitartrate 50 mg and 150 mg capsules Q6H; oral; 9 weeks	43	12 (6 – 26) years	Male: 56 Female: 44
Study 04	Multi-center, long-term, open label	PROCYSBI Q12H; oral; Mean (SD) Days of Exposure: 1089 (394.4) Min, Max: 35, 1677	60	10.9 (2 – 32) years	Male: 63 Female: 37

The safety and efficacy of PROCYSBI have been established in pediatric patients (6 years of age and older) that were enrolled in Study 03, and patients aged 2 years and older that were enrolled in Study 04. In total, there were 53/62 (86%) of patients who received PROCYSBI during these clinical studies in the pediatric age range of 2 to < 18 years. There were no patients enrolled in the clinical trials over the age of 65 years.

Study 03: Multi-Center, Open-Label, Randomized Clinical Trial

Study demographics and trial design

This clinical trial comparing immediate-release cysteamine bitartrate and PROCYSBI was conducted in 43 (40 pediatric and 3 adult) patients with nephropathic cystinosis. All but one patient were Caucasian (Per Protocol Population).

WBC cystine levels were measured using the mixed leukocyte assay. Patients with WBC cystine concentrations greater than 2 nmol $\frac{1}{2}$ cystine/mg protein and estimated glomerular filtration rate (eGFR corrected for body surface area) less than 30 mL/minute/1.73 m² at the time of screening were excluded from the trial. Prior to randomization, patients were to be on a stable dose of immediate-release cysteamine bitartrate administered every six hours. PROCYSBI dose adjustments of up to approximately 100% of the total daily dose of immediate-release cysteamine bitartrate were allowed by trial criteria. The average total daily dose of PROCYSBI for patients completing the clinical trial was approximately 82% of the average total daily dose of immediate-release cysteamine bitartrate for patients at trial entry. There were 24/43 (56%) patients who had their dose of PROCYSBI up-titrated by the end of the 3 week treatment period.

The primary endpoint of the study was a non-inferiority comparison of PROCYSBI to immediate-release cysteamine bitartrate in terms of control of WBC cystine levels.

Study results

This trial demonstrated that at steady-state, PROCYSBI administered every 12 hours (over a 3 week period) was non-inferior to immediate-release cysteamine bitartrate administered every 6 hours (over a 3 week period) with respect to the depletion of WBC cystine concentrations (Table 8).

Table 8: Primary Analysis^a of WBC Cystine in Study 03 (Per Protocol Population)

	Immediate-release cysteamine bitartrate	PROCYSBI
WBC cystine concentration in nmol $\frac{1}{2}$ cystine/mg protein ^b (LS Mean \pm SE)	0.44 \pm 0.06	0.52 \pm 0.06
Difference in Treatment effect (LS mean \pm SE) [95.8% CI]	0.08 \pm 0.03 [0.01 to 0.15] ^c	

^a Statistical analysis performed using non-linear mixed models.

^b Measured using the mixed leukocyte assay.

^c Non-inferiority margin was 0.3 nmol $\frac{1}{2}$ cystine/mg protein.

CI = confidence interval; LS = least squares; SE = standard error; WBC = white blood cell.

Study 04: Multi-Center, Single-Arm, Open-Label, Long-Term Extension Clinical Trial

Study demographics and trial design

Study 04 is a long-term, open-label study of the safety, tolerability and steady-state pharmacokinetics and pharmacodynamics of PROCYSBI in pediatric and adult cystinosis patients. Additional enrollment in Study 04 was opened to subjects ≤ 6 years of age and kidney transplant recipients. The estimated mean duration of exposure for subjects who continued in Study 04 after completing Study 03, for subjects newly enrolled in Study 04 who were ≤ 6 years of age, or who had previously received a kidney transplant was approximately 3.3 years (1191 days), 2.5 years (902 days), and 2.2 years (815 days), respectively.

Table 9: Mean WBC Cystine (nmol $\frac{1}{2}$ cystine/mg protein) over Time (Study 04 Pharmacokinetics/Pharmacodynamics Population)

Visit	Approx. Years in Study RP103-04	Statistic	Subpopulation		
			RP103-03 (N=40)	≤ 6 Years of Age (N=13)	Transplant (N=6)
			WBC cystine (nmol $\frac{1}{2}$ cystine/mg protein) ^a at 0.5 hour post-RP103 dose		
First visit (M1 or D1) ^b	0-0.1 year	Mean (SD) [n]	0.43 (0.513) [n=39]	1.41 (1.030) [n=13]	2.40 (1.687) [n=5]
M6	0.5 year	Mean (SD) [n]	0.46 (0.431) [n=38]	2.00 (1.729) [n=13]	1.75 (1.242) [n=5]
Q2	1.0 year	Mean (SD) [n]	0.42 (0.352) [n=38]	1.10 (0.578) [n=12]	1.28 (0.830) [n=5]
Q4	1.5 years	Mean (SD) [n]	0.49 (0.344) [n=37]	1.31 (1.480) [n=11]	1.57 (0.944) [n=4]
Q6	2.0 years	Mean (SD) [n]	0.52 (0.304) [n=35]	1.40 (2.188) [n=6]	0.62 (0.368) [n=3]
Q8	2.5 years	Mean (SD) [n]	0.44 (0.371) [n=29]	0.98 (0.487) [n=6]	0.84 (0.550) [n=3]
Q10	3.0 years	Mean (SD) [n]	0.39 (0.290) [n=20]	0.90 (0.386) [n=3]	1.69 (0.682) [n=3]
Q13	3.75 years	Mean (SD) [n]	0.54 (0.393) [n=19]	N/A	N/A

^a Measured using the mixed leukocyte assay.

^b First available visit in Study RP103-04: Month 1 for subjects from Study 03 and Day 1 for the other two subpopulations. Visits shown are first visit and visits at approximately half-yearly increments through approximately 4 years.

D = day; M = month(ly) visit; N/A = not applicable; Q = quarter(ly) visit; SD = standard deviation; WBC = white blood cell.

In this study, all but one subject were Caucasian. Subjects from the transplant subpopulation tended to be older than subjects from the other two subpopulations (median age at baseline in the

transplant subpopulation was 20.5 years compared to 5.0 years in the subpopulation of subjects \leq 6 years of age and 11.0 years in the subpopulation of subjects who completed RP103-03).

Study results

WBC cystine levels were measured using the mixed leukocyte assay. The mean WBC cystine level for Study 03 patients at the first available visit in Study 04 was below 1.0 nmol $\frac{1}{2}$ cystine/mg protein (mean of 0.43) reflecting the WBC cystine control achieved in Study 03 as shown in Table 8. Mean WBC cystine levels remained below 1.0 through the duration of the study (mean of 0.54 at approximately 3.75 years; see Table 9).

DETAILED PHARMACOLOGY

In Vitro Drug Interaction Studies

In vitro data indicate cysteamine bitartrate is a substrate of P-gp and OCT2 but not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT1.

In vitro data indicate cysteamine bitartrate is not an inhibitor of CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). The potential for cysteamine to affect the pharmacokinetics of other drugs via these enzymes is low.

In vitro data indicate cysteamine bitartrate is not an inhibitor of uptake transporters OATP1B1, 1B3, OAT1, OAT3, OCT1 and OCT2 and efflux transporters P-gp and BCRP.

Pharmacodynamics and Pharmacokinetics

Cysteamine is an aminothiols that participates in a thiol-disulfide interchange reaction within lysosomes converting cystine into cysteine and cysteine-cysteamine mixed disulfide, both of which can exit the lysosome via the lysine transporter in patients with cystinosis.

The findings from *in vitro* and *in vivo* studies confirm the cystine depletion properties of cysteamine. Cysteamine also dose-dependently depletes brain somatostatin, noradrenaline, and pituitary/serum prolactin.

The pharmacokinetics of PROCYSBI were evaluated in 43 patients with cystinosis and with an estimated glomerular filtration rate of > 30 mL/minutes/1.73m² (Study 03). The mean C_{max}, AUC_{inf} and T_{max} were 3.6 mg/L, 726 min*mg/L and 188 minutes, respectively.

TOXICOLOGY

Repeated-Dose Study

Species	Route	Duration	Doses (mg/kg/day)	Results
Sprague-Dawley Rats	Oral (gavage)	14 days (once daily)	0, 75, 150, 300 ^a	Duodenal transmural ulceration (with perforation) was observed in one 300 mg/kg/day female, as well as gastric submucosal inflammation with edema and/or erosion/ulcerations at ≥ 150 mg/kg/day. The NOAEL is 75 mg/kg/day; however, one male had a depressed area in the stomach mucosa with submucosal inflammation but no ulceration.
Rhesus Monkeys	Stomach Tube	4 weeks	150 ^b	On the basis of the observed changes of sedation and tachycardia, central nervous and cardiovascular systems could be the target organs of toxicity and a dose of 150 mg/kg/day was toxic. Cysteamine use of up to 4 weeks did not improve tolerability.
Rhesus Monkeys	Stomach Tube	58 weeks	Group 1: 0 Group 2: 20 ^b Group 3: 20 to 150 ^b	One animal of five died in the dose titration group at a dose of 35 mg/kg in Week 6 of the study; this animal showed esophageal ulceration and hepatic toxicity. The gastrointestinal tract and liver are the target organs of toxicity. An oral dose of 20 mg/kg/day (0.2-fold the recommended human maintenance dose based on body surface area) produced minimum effects and could be considered as the NOAEL for this study.
Wistar rats	Oral (drinking water)	6 months	Group 1: 0 mg/day Group 2: 3 mg/day	Group 2 demonstrated skeletal and cardiovascular toxicity. Vertebral bodies were collapsed at the thoracolumbar junction and the midthoracic region, resulting in kyphosis. Longitudinal dissection of the aorta was seen histologically; degeneration of elastic fibers led to aortic aneurysm and rupture.
Long Evans neonatal rats	Subcutaneous	8-11 days	Group 1: 0 Group 2: 100-250 Group 3: 200	High mortality; delayed growth, eye opening, and sexual development; and permanent bilateral cataracts were observed in treated pups.
Sprague Dawley neonatal rats	Subcutaneous	6 days	Group 1: 0 Group 2: 200 (day 1-6) Group 3: 0 (day 10-16) Group 4: 200 (day 10-16)	Cataract formation was seen in neonatal rats dosed with cysteamine hydrochloride for the first six days of life. However, delayed exposure of neonatal rats to cysteamine (treatment day 10 through 16) resulted in the absence of cataract formation.

AUC_{0-last} = area under the curve from time zero to last time point; C_{max} = maximum concentration; NOAEL = No Observed Adverse Effect Level.

^a Represents free base using a correction factor of 3.3445.

^b Represents free base.

Reproductive Toxicity

Reproduction studies with cysteamine have been performed in pregnant rats at oral doses of 37.5, 75, 100, and 150 mg/kg/day. Doses of 100 and 150 mg/kg/day produce adverse effects on the fetus during organogenesis resulting in intrauterine growth retardation, fetal death, and malformations. Observed teratogenic findings were cleft palate vertebrae kyphosis, heart ventricular septal defects, and microcephaly. Cysteamine ≥ 100 mg/kg/day (about 0.5 times the recommended human maintenance dose based on body surface area) was fetotoxic and teratogenic. The NOAEL was considered to be 75 mg/kg/day (about 0.4 times the recommended human maintenance dose based on body surface area).

In a fertility and early embryonic development study in rats, orally administered cysteamine at 150 mg/kg/day (900 mg/m² per day, 0.7 times the recommended human maintenance dose based on body surface area) had no significant effects on the duration of estrous cycle, number of females who became pregnant, number of corpora lutea, number of implantation sites, or number of failed conceptions. In another study, an oral dose of 375 mg/kg per day (2250 mg/m² per day, 1.7 times the recommended human maintenance dose based on body surface area), reduced the conception rate of the adult rats and the number of live births per litter.

In pre and postnatal development studies in rats, orally administered cysteamine at 375 mg/kg/day (2250 mg/m² per day, 1.7 times the recommended human maintenance dose based on body surface area) demonstrated post-natal toxicity. Pups nursed by females treated at this dose had growth retardation and reduced survival at weaning. No effects on pre and postnatal development were observed at 75 mg/kg per day (450 mg/m² per day, 0.4 times the recommended human dose based on body surface area).

Genotoxicity

Cysteamine was not mutagenic in bacterial reverse mutational assays (Ames tests). In *in vitro* assays for clastogenicity, cysteamine induced chromosome aberrations (in rat liver cells and human lymphocytes), and sister chromatid exchanges (in Chinese hamster cells but not human lymphocytes). Cysteamine was negative in an *in vivo* mouse micronucleus test.

Carcinogenesis

Cysteamine has not been tested for its carcinogenic potential in long-term animal studies.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PROCYSBI™

Cysteamine delayed-release capsules

Read this carefully before you start taking **PROCYSBI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PROCYSBI**.

What is PROCYSBI used for?

PROCYSBI is used for treatment of nephropathic cystinosis.

How does PROCYSBI work?

Nephropathic cystinosis is a rare disease where the amino acid cystine builds up in organs and tissues, causing damage. PROCYSBI changes cystine so that it does not build up in the organs and tissues.

What are the ingredients in PROCYSBI?

Medicinal ingredient: Cysteamine bitartrate (also called mercaptamine bitartrate)

Non-medicinal ingredients:

Capsule Contents: Hypromellose, methacrylic acid copolymer, microcrystalline cellulose, purified water, sodium lauryl sulfate, talc and triethyl citrate.

Capsule Shell Ingredients: FD&C Blue#2, gelatin and titanium dioxide.

PROCYSBI comes in the following dosage forms:

Delayed-release capsules, 25 mg and 75 mg.

Do not use PROCYSBI if you:

- are allergic to cysteamine bitartrate or to any of the ingredients in PROCYSBI.
- are allergic to penicillamine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PROCYSBI.

Talk about any health conditions or problems you may have, including if you:

- have skin or bone problems including rashes, stretch marks, fractures, painful joints.
- have a serious skin rash including severe skin peeling especially mouth and eyes, red or purple rash, flu-like symptoms.
- have or have had stomach or bowel (intestinal) problems including ulcers or bleeding or changes in stomach or bowel problems.
- have a history of seizures, lack of energy, unusual sleepiness, depression, ringing in the ear, double vision, loss of vision, pain behind the eye or pain with eye movement or changes in

- your ability to think clearly.
- have liver or blood problems.
 - have any other medical conditions.
 - are pregnant or plan to become pregnant. PROCYSBI might harm your unborn baby. Tell your healthcare professional right away if you think that you are pregnant. Talk with your healthcare professional about the benefits and risks of taking PROCYSBI during pregnancy. You should also discuss the importance of using birth control during your treatment with PROCYSBI. Your healthcare professional can tell you which birth control options are best for you.
 - are breastfeeding or plan to breastfeed. You should not breastfeed during treatment with PROCYSBI. Talk with your healthcare professional about the best way to feed your baby if you take PROCYSBI.

Other warnings you should know about:

Driving and using machines

Do not drive or operate heavy machinery until you know how PROCYSBI affects you. PROCYSBI can make you sleepy or less alert than normal.

If you are currently taking cysteamine eye drops, do not stop taking them without talking to your healthcare professional since PROCYSBI does not prevent deposits of cystine crystals in the eye.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PROCYSBI:

- Bicarbonates and proton pump inhibitors used to reduce stomach acid.
- Do not take with alcohol.

How to take PROCYSBI:

- PROCYSBI should be taken exactly as you are told by your healthcare professional.
- Your healthcare professional will do blood tests before you start treatment with PROCYSBI to decide on the dose that is best for you. You will also have blood tests regularly while you are taking PROCYSBI.
- Your healthcare professional may start you on a low dose of PROCYSBI, and slowly increase your dose to help avoid side effects, especially if you have not taken a medicine that contains cysteamine bitartrate before.
- Do not change your dose of PROCYSBI unless you are told to by your healthcare professional.
- PROCYSBI should be taken without food. Do not eat for at least 2 hours before taking PROCYSBI and 2 hours after. If this is not possible, food can be eaten 30 minutes after taking PROCYSBI.
- Avoid eating foods that are high in fat and protein (e.g. dairy) close to the time that you will take a dose of PROCYSBI.
- Swallow PROCYSBI capsules whole with orange juice. Do not crush or chew

PROCYSBI or the capsule contents.

- For children who are at risk of choking on the capsules (approximately 6 years of age and younger) and for adults who cannot swallow the capsules whole, the capsules can be opened and the capsule contents taken with applesauce (see instructions below). PROCYSBI can also be given through a gastrostomy tube, size 14 French or larger (see instructions below).

Taking PROCYSBI with applesauce:

Do not take PROCYSBI with any food other than applesauce.

- Step 1: Place about ½ cup (4 ounces) of applesauce into a clean container. Do not use any other food.
- Step 2: Open the PROCYSBI capsule. You may need to use more than 1 PROCYSBI capsule for the dose prescribed by your healthcare professional.
- Step 3: Sprinkle the granules that are inside of the capsule or capsules onto the applesauce.
- Step 4: Mix the granules with the applesauce.
- Step 5: Swallow the applesauce and granule mixture within 30 minutes of mixing. Do not chew the granules. Do not save the applesauce and granules for later use.

Giving PROCYSBI through a gastrostomy tube (G-tube) size 14 French or larger:

- It is best to use a straight (bolus) feeding tube.

Use only strained applesauce with no chunks when giving PROCYSBI through a gastrostomy tube (G-tube).

- Step 1: Flush the gastrostomy tube button with 5 mL of water to clear the button.
- Step 2: Place about ½ cup (4 ounces) of applesauce into a clean container. Use at least 1/8 cup (1 ounce) of applesauce for children 25 kg or less starting PROCYSBI at a dose of 1 or 2 capsules.
- Step 3: Open the PROCYSBI capsule. You may need to use more than 1 PROCYSBI capsule for the dose prescribed by your healthcare professional.
- Step 4: Sprinkle the granules that are inside the capsule or capsules on the applesauce. Gently mix the granules with the applesauce.
- Step 5: Place the tip of a catheter tip syringe at the bottom of the container of applesauce and granule mixture. For an adult dose, draw up about 40 mL of the mixture. When giving to a child, draw up at least 10 mL of the mixture for doses of 1 or 2 capsules.
- Step 6: Place the tip of the catheter tip syringe into the feeding tube that will be connected to the gastrostomy tube. Fill the feeding tube with the applesauce and granule mixture.
- Step 7: Hold the feeding tube in a horizontal (straight across) position. Give the applesauce and granule mixture through the gastrostomy tube at a quick and steady rate of 10 mL over 10 seconds.
- Step 8: Repeat Steps 5 through Step 7 until all of the applesauce and granule mixture is given.
Give all of the applesauce and granule mixture through the gastrostomy tube within 30 minutes of mixing. Do not save the applesauce and granule mixture for later use.
- Step 9: Draw up at least 10 mL of orange juice into another catheter tip syringe. Gently swirl the syringe. Flush the gastrostomy tube with the orange juice. Use enough orange juice to

flush the gastrostomy tube so that there is no applesauce and granule mixture left in the gastrostomy tube.

Usual dose:

Your healthcare professional will tell you how many PROCYSBI capsules to take. PROCYSBI is taken 2 times each day, every 12 hours.

Overdose:

If you think you have taken too much PROCYSBI, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as possible. If it is within 4 hours of the time the next dose is due, skip the missed dose. Take the next dose at your regularly scheduled time. Do not take 2 doses at one time to make up for a missed dose.

What are possible side effects from using PROCYSBI?

These are not all the possible side effects you may feel when taking PROCYSBI. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects with PROCYSBI include:

- vomiting
- nausea
- stomach (abdominal) pain and discomfort
- loss of appetite
- breath odour
- diarrhea
- skin odour
- tiredness
- skin rash
- headache
- dizziness
- flushing

PROCYSBI can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

The following serious side effects, as presented in the table, have been observed with cysteamine (as an immediate release formulation or PROCYSBI).

Serious side effects and what to do about them			
Symptom/effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON Stomach and bowel (intestinal) problems: flu-like symptoms like fever, vomiting and diarrhea.		✓	
UNCOMMON Central nervous system symptoms: seizures, depression, becoming very sleepy, headache, ringing in the ears, dizziness, double vision, loss of vision, pain behind the eye or pain with eye movement.		✓	
Ehlers-Danlos-like Syndrome: Purplish marks on the skin, streaking of the skin, bone problems (including thinning of the bones, spine fractures, curvature of the spine, and "knock knees"), leg pain, and hyperextension of the joints.		✓	
Hypersensitivity reactions: hives, difficulty breathing, swelling of face, lips, tongue, and/or throat.			✓
Kidney problems: swollen hands or legs, or unusual weight gain, decreased urination.		✓	
Stomach and bowel (intestinal) problems: vomiting blood or blood in the stool (ulcers).			✓
VERY RARE Serious skin reactions: any combination of red itchy rash with blisters and peeling of the skin and/or of the lips, eyes, mouth, nasal passages or genitals (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, hypersensitivity Syndrome). It often goes with fever, chills, headache, cough, body aches or joint pain. You may have dark urine, yellow skin or eyes.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store PROCYSBI at room temperature between 20 °C to 25 °C and in a dry place away from light.
- Dispose of capsules by the “Use by” date entered by the pharmacist on bottle.
- Discard expired capsules per your local or provincial regulations.
- Keep PROCYSBI tightly closed in the original bottle.

The 25 mg PROCYSBI bottle contains one desiccant canister and one oxygen absorber canister. The 75 mg PROCYSBI bottle contains one desiccant canister and two oxygen absorber canisters. Do not eat or throw away the desiccant canister or oxygen absorber canister(s).

Keep out of reach and sight of children.

If you want more information about PROCYSBI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website <http://www.hc-sc.gc.ca>, the manufacturer’s website <http://www.horizontherapeutics.ca>, or by calling 1-844-380-7850.

This leaflet was prepared by Horizon Pharma Ireland Ltd.

Last Revised June 08, 2017.

ATTACHMENT 2



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Notice of Compliance date:

2017-06-13

Manufacturer:

HORIZON PHARMA IRELAND LTD

Product type:

Prescription Pharmaceutical

NOC with conditions:

No

Submission type:

New Drug Submission (NDS)

Submission class:

Priority-NAS

Brand 1 of 1 :

PROCYSBI

Product 1 of 2 :

Drug identification number: 02464705

Dosage form(s): Capsule (Delayed Release)

Route(s) of administration: Oral

Medicinal ingredient(s):

Ingredient	Strength
CYSTEAMINE BITARTRATE	25 MG/CAP

Product 2 of 2 :

Drug identification number: 02464713

Dosage form(s): Capsule (Delayed Release)

Route(s) of administration: Oral

Medicinal ingredient(s):

Ingredient	Strength
CYSTEAMINE BITARTRATE	75 MG/CAP

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ATTACHMENT 3



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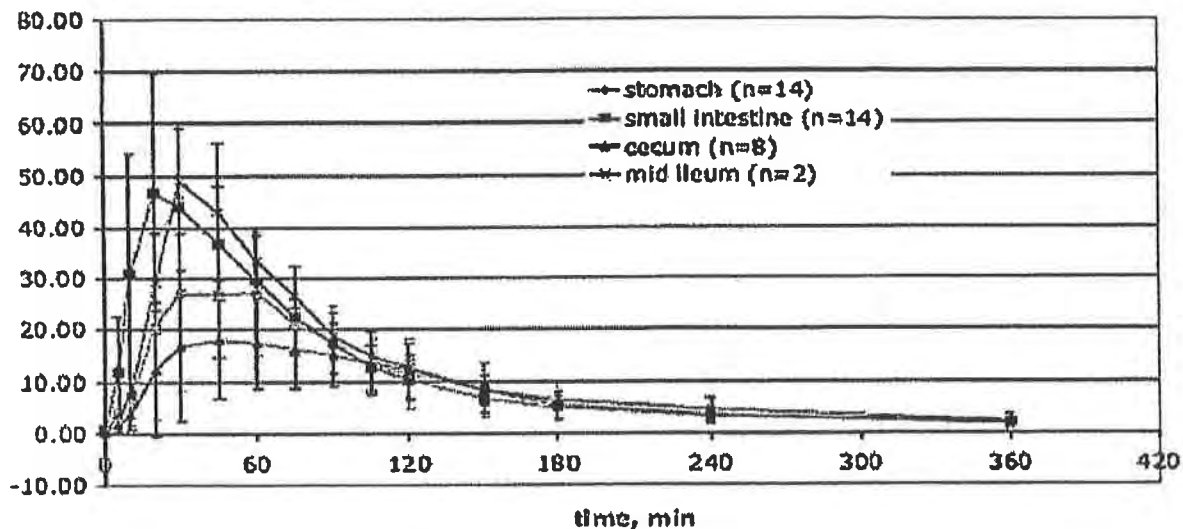
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(54) Titre : CYSTEAMINE A ENROBAGE ENTERIQUE, CYSTAMINE ET LEURS DERIVES
(54) Title: ENTERICALLY COATED CYSTEAMINE, CYSTAMINE AND DERIVATIVES THEREOF



(57) Abrégé/Abstract:

The disclosure provides oral cysteamine and cystamine formulations useful for treating cystinosis and neurodegenerative diseases and disorders. The formulations provide controlled release compositions that improve quality of life and reduced side-effects.



**ENTERICALLY COATED CYSTEAMINE, CYSTAMINE AND DERIVATIVES
THEREOF**

[0001]

FIELD OF THE INVENTION

[0002] The invention relates to methods, compositions and treatments for metabolic conditions and free radical damage. More specifically, the invention relates to methods and composition useful for treating Cystinosis and neurodegenerative diseases such as Huntington's; Alzheimer's and Parkinson's disease, as free radical and radioprotectants, and as hepto-protectant agents.

BACKGROUND

[0003] Cystinosis is a rare, autosomal recessive disease caused by intra-lysosomal accumulation of the amino acid cystine within various tissues, including the spleen, liver, lymph nodes, kidney, bone marrow, and eyes. Nephropathic cystinosis is associated with kidney failure that necessitates kidney transplantation. To date, the only specific treatment for nephropathic cystinosis is the sulfhydryl agent, cysteamine. Cysteamine has been shown to lower intracellular cystine levels, thereby reducing the rate of progression of kidney failure in children.

[0004] Cysteamine, through a mechanism of increased gastrin and gastric acid production, is ulcerogenic. When administered orally to children with cystinosis, cysteamine has also been shown to cause a 3-fold increase in gastric acid production and a 50% rise of serum gastrin levels. As a consequence, subjects that use cysteamine suffer gastrointestinal (GI) symptoms and are often unable to take cysteamine regularly or at full dose.

[0005] To achieve sustained reduction of leukocyte cystine levels, patients are normally required to take oral cysteamine every 6 hours, which invariably means having to awaken from sleep. However, when a single dose of cysteamine was administered intravenously the leukocyte cystine level remained suppressed for more than 24 hours, possibly because plasma cysteamine concentrations were higher and achieved more rapidly than when the drug is administered orally. Regular intravenous administration of cysteamine would not be practical. Accordingly, there is a need for formulations and delivery methods that would result in higher plasma, and thus intracellular, concentration as well as decrease the number of daily doses and therefore improve the quality of life for patients.

SUMMARY

[0006] The invention provides a composition comprising an enterically coated cystamine or cystamine derivative.

[0007] The invention also provides a composition comprising an enterically coated cysteamine or cysteamine derivative.

[0008] The invention further provides a composition comprising a coated cystinosis therapeutic agent that has increased uptake in the small intestine compared to a non-coated cystinosis therapeutic agent when administered orally. In one aspect, the coated cystinosis therapeutic agent comprises a cysteamine or cysteamine derivative.

[0009] The invention also provides a method of treating a subject with cystinosis, comprising administering to the subject a composition of the invention.

[0010] The invention also contemplates a method of treating a subject with a neurodegenerative disease or disorder comprising administering to the subject a composition of the invention comprising an enterically coated cystamine or cystamine derivative.

[0011] The invention provides a pharmaceutical formulation comprising a composition of the invention further including various pharmaceutically acceptable agents (e.g., flavorants, binders and the like) in a pharmaceutically acceptable carrier.

[0012] The invention provides a method of treating cystinosis or a neurodegenerative disease or disorder comprising administering a composition of the invention and a second therapeutic agent.

BRIEF DESCRIPTION OF THE FIGURES

[0013] Figure 1 shows enterocolonic tube. (A) Is an abdominal X-ray film showing the radiopaque weighted tip of the tube entering the ascending colon. (B) Is a contrast infused picture. The tube has passed through the small intestine and the tip is confirmed.

[0014] Figure 2 shows mean plasma cysteamine levels taken from patients with cystinosis and control subjects after delivery of drug into various intestinal sites. Error bars are standard error of the mean. In 2 control subjects, most distal point of drug delivery was the mid-ileal region.

[0015] Figure 3 shows the mean change in leukocyte cystine levels, compared with baseline levels, over a 12-hour period following delivery of cysteamine into varying intestinal sites. Negative levels signify increased leukocyte cystine depletion compared with baseline.

[0016] Figure 4 shows a scatterplot of plasma cysteamine C_{max} vs. AOC of WBC Cystine changes from Baseline. Positive value means decrease from baseline. Negative value means increase from baseline. AOC change from baseline was affected by C_{max} for cysteamine ($P < .001$).

[0017] Figure 5 shows serial leukocyte cystine levels after drug was given as normal Cystagon and enteric-coated (EC) cysteamine on alternate days. These serial levels were taken during the inpatient phase of the study. Desired

cystine levels are below 1 mmol 1/2cystine/mg protein. Higher dose enteric-coated (yellow)) drug resulted in prolonged cystine suppression with 12 hour levels still within desired range.

[0018] Figure 6 shows the blood cysteamine levels following a single 450mg dose of Cystagon (series 1), 450mg EC-cysteamine (series 2) and 900mg EC-cysteamine (series 3). The C_{max} is higher following EC drug. In addition, the time to C_{max} is longer following EC-drug, suggesting that the drug is released from the capsule within the small intestine rather than the stomach.

DETAILED DESCRIPTION

[0019] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a derivative" includes a plurality of such derivatives and reference to "a subject" includes reference to one or more subjects known to those skilled in the art, and so forth.

[0020] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice of the disclosed methods and compositions, the exemplary methods, devices and materials are described herein.

[0021] The publications discussed above and throughout the text are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior disclosure.

[0022] Cystinosis is a metabolic disease characterized by an abnormal accumulation of the amino acid cystine in various organs of the body such as the kidney, eye, muscle, pancreas, and brain. Different organs are affected at different ages.

[0023] There are three clinical forms of cystinosis. Infantile (or nephropathic) cystinosis; late-onset cystinosis; and benign cystinosis. The latter form does not produce kidney damage. Infantile cystinosis is usually diagnosed between 6 and 18 months of age with symptoms of excessive thirst and urination, failure to thrive, rickets, and episodes of dehydration. These findings are caused by a disorder called renal tubulopathy or Fanconi syndrome. As a consequence important nutrients and minerals are lost in the urine. Children with cystinosis also have crystals in their eyes (after one year of age) which may lead to photosensitivity. They also have an increased level of cystine in their white blood cells without adverse effect but allowing the diagnosis to be ascertained. Without specific treatment, children with cystinosis develop end-stage renal failure, i.e., lose their kidney function, usually between 6 and 12 years of age. Without cysteamine treatment subjects can develop complications in other organs due to the continued accumulation of cystine throughout the body. These complications can include muscle wasting, difficulty swallowing, diabetes, and hypothyroidism.

[0024] Some symptoms include the inability of the kidneys to concentrate urine and allow important quantities of sodium, potassium, phosphorus, bicarbonate and substances like carnitine to be excreted in the urine. Treatment of symptoms compensates for these urinary losses. Subjects need to drink large quantities of water, because up to 2 to 3 liters of water are lost in the urine every day driving the feeling of being thirsty. In addition, the loss of urinary

electrolytes (sodium, potassium, bicarbonate, phosphorus) must be compensated in the subject. It is often necessary to add a salt supplement in the form of sodium chloride. Children also lose bicarbonate and potassium in the urine, which can be compensated for by giving sodium bicarbonate and potassium bicarbonate.

[0025] Specific treatments of cystinosis aim to reduce cystine accumulation within the cells. Cystinosis is currently treated with cysteamine (Cystagon™). Cysteamine also improves growth of cystinosis children. Cysteamine is only active in a very short period of time not exceeding 5-6 hours, thus requiring administration of Cystagon™ capsules 4 times a day, that is to say about every 6 hours. This treatment is also only effective if continued day after day, indefinitely in order to control the disease. About 1000 children require lifelong treatment to prolong their lives and prevent deterioration of kidney function. However, as mentioned above, cysteamine administration results in increased gastric secretions and is ulcerogenic. In addition, routes and timing of administration provide difficulty for subjects in need of such therapy. Recently, a similar drug called cystamine (the disulfide form of cysteamine) has been studied for neurodegenerative disorders including Huntington's and Parkinson's diseases. Cystamine has similar side-effects and dosing difficulties to that of cysteamine.

[0026] Cysteamine is a potent gastric acid-secretagogue that has been used in laboratory animals to induce duodenal ulceration; studies in humans and animals have shown that cysteamine-induced gastric acid hypersecretion is most likely mediated through hypergastrinemia. In previous studies performed in children with cystinosis who suffered regular upper gastrointestinal symptoms, a single oral dose of cysteamine (11-23 mg/kg) was shown to cause

hypergastrinemia and a 2-to 3-fold rise in gastric acid-hypersecretion. Symptoms suffered by these individuals included abdominal pain, heartburn, nausea, vomiting, and anorexia. The disclosure demonstrates that cysteamine-induced hypergastrinemia arises, in part, as a local effect on the gastric antral-predominant G-cells in susceptible individuals. The data also suggest that this is also a systemic effect of gastrin release by cysteamine. Depending upon the route of administration, plasma gastrin levels usually peak after intragastric delivery within 30 minutes, whereas the plasma cysteamine levels peak later.

[0027] Subjects with cystinosis are required to ingest oral cysteamine (Cystagon) every 6 hours, day and night. When taken regularly, cysteamine can deplete intracellular cystine by up to 90% (as measured in circulating white blood cells), and this has been shown to reduce the rate of progression to kidney failure/transplantation and also to obviate the need for thyroid replacement therapy. Unfortunately, because of the strict treatment regimen and the associated symptoms, nonadherence with cysteamine therapy remains a problem, particularly among adolescent and young adult patients. By reducing the frequency of required cysteamine dosing, adherence to a therapeutic regimen can be improved. The disclosure demonstrates that delivery of cysteamine to the small intestine reduces gastric distress and ulceration and improves bioavailability of cysteamine in the circulation. Delivery of cysteamine into the small intestine is useful due to improved absorption rate from the SI, greater surface area of the SI, and/or less cysteamine undergoing hepatic first pass elimination when absorbed through the small intestine. This disclosure shows a dramatic decrease in leukocyte cystine within an hour of cysteamine delivery.

[0028] In addition, sulfhydryl (SH) compounds such as cysteamine, cystamine, and glutathione are among the most important and active intracellular antioxidants. Cysteamine protects animals against bone marrow and gastrointestinal radiation syndromes. The rationale for the importance of SH compounds is further supported by observations in mitotic cells. These are the most sensitive to radiation injury in terms of cell reproductive death and are noted to have the lowest level of SH compounds. Conversely, S-phase cells, which are the most resistant to radiation injury using the same criteria, have demonstrated the highest levels of inherent SH compounds. In addition, when mitotic cells were treated with cysteamine, they became very resistant to radiation. It has also been noted that cysteamine may directly protect cells against induced mutations. The protection is thought to result from scavenging of free radicals, either directly or via release of protein-bound GSH. An enzyme that liberates cysteamine from coenzyme A has been reported in avian liver and hog kidney. Recently, studies have appeared demonstrating a protective effect of cysteamine against the hepatotoxic agents acetaminophen, bromobenzene, and phalloidine.

[0029] Cystamine, in addition, to its role as a radioprotectant, has been found to alleviate tremors and prolong life in mice with the gene mutation for Huntington's disease (HD). The drug may work by increasing the activity of proteins that protect nerve cells, or neurons, from degeneration. Cystamine appears to inactivate an enzyme called transglutaminase and thus results in a reduction of huntingtin protein (Nature Medicine 8, 143-149, 2002). In addition, cystamine was found to increase the levels of certain neuroprotective proteins. However, due to the current methods and formulation of delivery of cystamine, degradation and poor uptake require excessive dosing.

[0030] The disclosure is not limited with respect to a specific cysteamine or cystamine salt or ester or derivative; the compositions of the disclosure can contain any cysteamine or cystamine, cysteamine or cystamine derivative, or combination of cysteamine or cystamines. The active agents in the composition, *i.e.*, cysteamine or cystamine, may be administered in the form of a pharmacologically acceptable salt, ester, amide, prodrug or analog or as a combination thereof. Salts, esters, amides, prodrugs and analogs of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," 4th Ed. (New York: Wiley-Interscience, 1992). For example, basic addition salts are prepared from the neutral drug using conventional means, involving reaction of one or more of the active agent's free hydroxyl groups with a suitable base. Generally, the neutral form of the drug is dissolved in a polar organic solvent such as methanol or ethanol and the base is added thereto. The resulting salt either precipitates or may be brought out of solution by addition of a less polar solvent. Suitable bases for forming basic addition salts include, but are not limited to, inorganic bases such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine, or the like. Preparation of esters involves functionalization of hydroxyl groups which may be present within the molecular structure of the drug. The esters are typically acyl-substituted derivatives of free alcohol groups, *i.e.*, moieties which are derived from carboxylic acids of the formula $R-COOH$ where R is alkyl, and typically is lower alkyl. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures. Preparation of amides and prodrugs

can be carried out in an analogous manner. Other derivatives and analogs of the active agents may be prepared using standard techniques known to those skilled in the art of synthetic organic chemistry, or may be deduced by reference to the pertinent literature.

[0031] The disclosure provides delivery methods and compositions that overcome the problems associated with cysteamine and cystamine delivery. The methods of compositions of the disclosure provide enteric-coated compositions that result in less frequent dosing (2X/day vs. 4X/day), increased patient compliance and fewer gastrointestinal side effects (e.g., pain, heartburn, acid production, vomiting) and other side effects (e.g., patients smell like rotten eggs - a particular compliance problem as subjects reach puberty). The disclosure provides enteric-coated cysteamine compositions (sulfhydryl/Cystagon™) and cystamine compositions.

[0032] The disclosure provides methods for the treatment of cystinosis, the treatment of neurodegenerative disease such as Alzheimer Disease, Huntington's and Parkinson's disease and free radical damage using enterically coated cysteamine and cystamine, respectively.

[0033] The disclosure provides composition comprising enterically formulated cysteamine and cystamine derivatives. Examples of cysteamine derivatives include hydrochloride, bitartrate and phosphocysteamine derivatives. Cystamine and cystamine derivatives include sulfated cystamine. Enteric coatings prolong release until the cystamine, cystamine derivative, or cysteamine derivative/Cystagon™ reaches the intestinal tract, typically the small intestine. Because of the enteric coatings, delivery to the small intestine is improved thereby improving uptake of active ingredient while reducing gastric side effects. This will result in a reduction in the need for frequent administration that

currently is associated with Cystagon therapy, cystamine and cysteamine therapy.

[0034] An "enterically coated" drug or tablet refers to a drug or tablet that is coated with a substance--i.e., with an "enteric coating"--that remains intact in the stomach but dissolves and releases the drug once the small intestine is reached.

[0035] As used herein "enteric coating", is a material, a polymer material or materials which encase the medicament core (e.g., cystamine, cysteamine, Cystagon). Typically, a substantial amount or all of the enteric coating material is dissolved before the medicament or therapeutically active agent is released from the dosage form, so as to achieve delayed dissolution of the medicament core. A suitable pH-sensitive polymer is one which will dissolve in intestinal juices at a higher pH level (pH greater than 4.5), such as within the small intestine and therefore permit release of the pharmacologically active substance in the regions of the small intestine and not in the upper portion of the GI tract, such as the stomach.

[0036] The coating material is selected such that the therapeutically active agent will be released when the dosage form reaches the small intestine or a region in which the pH is greater than pH 4.5. The coating may be a pH-sensitive materials, which remain intact in the lower pH environs of the stomach, but which disintegrate or dissolve at the pH commonly found in the small intestine of the patient. For example, the enteric coating material begins to dissolve in an aqueous solution at pH between about 4.5 to about 5.5. For example, pH-sensitive materials will not undergo significant dissolution until the dosage form has emptied from the stomach. The pH of the small intestine gradually increases from about 4.5 to about 6.5 in the duodenal bulb to about 7.2 in the distal portions of the

small intestine (ileum). In order to provide predictable dissolution corresponding to the small intestine transit time of about 3 hours (e.g., 2-3 hours) and permit reproducible release therein, the coating should begin to dissolve within the pH range of the duodenum, and continue to dissolve at the pH range within the small intestine. Therefore, the amount of enteric polymer coating should be sufficient to substantially dissolved during the approximate three hour transit time within the small intestine (e.g., the proximal and mid-small intestine).

[0037] Enteric coatings have been used for many years to arrest the release of the drug from orally ingestible dosage forms. Depending upon the composition and/or thickness, the enteric coatings are resistant to stomach acid for required periods of time before they begin to disintegrate and permit release of the drug in the lower stomach or upper part of the small intestines. Examples of some enteric coatings are disclosed in U.S. Pat. No. 5,225,202.

As set forth in U.S. Pat. No. 5,225,202, some examples of coating previously employed are beeswax and glyceryl monostearate; beeswax, shellac and cellulose; and cetyl alcohol, mastic and shellac, as well as shellac and stearic acid (U.S. Pat. No. 2,809,918); polyvinyl acetate and ethyl cellulose (U.S. Pat. No. 3,835,221); and neutral copolymer of polymethacrylic acid esters (Eudragit[™] L30D) (F. W. Goodhart et al., Pharm. Tech., pp. 64-71, April 1984); copolymers of methacrylic acid and methacrylic acid methylester (Eudragits), or a neutral copolymer of polymethacrylic acid esters containing metallic stearates (Mehta et al., U.S. Pat. Nos. 4,728,512 and 4,794,001). Such coatings comprise mixtures of fats and fatty acids, shellac and shellac derivatives and the cellulose acid phthlates, e.g., those having a free carboxyl content. See, Remington's at page 1590, and Zeitova et al.

(U.S. Pat. No. 4,432,966), for descriptions of suitable enteric coating compositions. Accordingly, increased adsorption in the small intestine due to enteric coatings of cystamine, cysteamine derivatives (including Cystagon) can result in improvements in cystinosis as well as neurodegenerative diseases including, for example, Huntington's disease.

[0038] Generally, the enteric coating comprises a polymeric material that prevents cysteamine or cystamine release in the low pH environment of the stomach but that ionizes at a slightly higher pH, typically a pH of 4 or 5, and thus dissolves sufficiently in the small intestines to gradually release the active agent therein. Accordingly, among the most effective enteric coating materials are polyacids having a pK_a in the range of about 3 to 5. Suitable enteric coating materials include, but are not limited to, polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose proprionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypopyl methylcellulose succinate, carboxymethyl ethylcellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers, typically formed from methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with copolymers of acrylic and methacrylic acid esters (Eudragit NE, Eudragit RL, Eudragit RS). For example, the enterically coating can comprise Eudragit L30D, triethylcitrate, and hydroxypropylmethylcellulose (HPMC), Cystagon® (or other cysteamine derivative), wherein the coating comprises 10 to 13% of the final product.

[0039] By "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" are meant materials that are suitable for oral administration and not biologically, or otherwise, undesirable, i.e., that may be administered to a subject along with an active ingredient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of a pharmaceutical composition in which it is contained.

[0040] Similarly, a "pharmaceutically acceptable" salt, ester or other derivative of an active agent comprise, for example, salts, esters or other derivatives which are not biologically or otherwise undesirable.

[0041] "Stabilizing agents" refer to compounds that lower the rate at which pharmaceutical degrades, particularly an oral pharmaceutical formulation under environmental conditions of storage.

[0042] By the terms "effective amount" or "therapeutically effective amount" of a enteric formulation of cysteamine or cystamine refers to a nontoxic but sufficient amount of the agent to provide the desired therapeutic effect. As will be pointed out below, the exact amount required will vary from subject to subject, depending on the age, weight, and general condition of the subject, the severity of the condition being treated, and the like. An appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using only routine experimentation.

[0043] In one aspect of the disclosure there is provided a stabilized pharmaceutical composition for administration of an cysteamine or cystamine, wherein the cysteamine or cystamine is enterically coated.

[0044] The cysteamine or cystamine is present in the composition in a therapeutically effective amount;

typically, the composition is in unit dosage form. The amount of cysteamine or cystamine administered will, of course, be dependent on the age, weight, and general condition of the subject, the severity of the condition being treated, and the judgment of the prescribing physician. Suitable therapeutic amounts will be known to those skilled in the art and/or are described in the pertinent reference texts and literature. In one aspect, the dose is administered twice per day at about 0.5-1.0 g/m² (e.g., 0.7-0.8 g/m²) body surface area. Current non-enterically coated doses are about 1.35 g/m² body surface area and are administered 4-5 times per day.

[0045] The enterically coated cysteamine or cystamine can comprise various excipients, as is well known in the pharmaceutical art, provided such excipients do not exhibit a destabilizing effect on any components in the composition. Thus, excipients such as binders, bulking agents, diluents, disintegrants, lubricants, fillers, carriers, and the like can be combined with the cysteamine or cystamine. For solid compositions, diluents are typically necessary to increase the bulk of a tablet so that a practical size is provided for compression. Suitable diluents include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar. Binders are used to impart cohesive qualities to a tablet formulation, and thus ensure that a tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, hydroxyethyl cellulose,

and the like), and Veegum. Lubricants are used to facilitate tablet manufacture; examples of suitable lubricants include, for example, magnesium stearate, calcium stearate, and stearic acid, and are typically present at no more than approximately 1 weight percent relative to tablet weight. Disintegrants are used to facilitate tablet disintegration or "breakup" after administration, and are generally starches, clays, celluloses, algin, gums or crosslinked polymers. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and the like. If desired, flavoring, coloring and/or sweetening agents may be added as well. Other optional components for incorporation into an oral formulation herein include, but are not limited to, preservatives, suspending agents, thickening agents, and the like. Fillers include, for example, insoluble materials such as silicon dioxide, titanium oxide, alumina, talc, kaolin, powdered cellulose, microcrystalline cellulose, and the like, as well as soluble materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride, sorbitol, and the like.

[0046] A pharmaceutical composition may also comprise a stabilizing agent such as hydroxypropyl methylcellulose or polyvinylpyrrolidone, as disclosed in U.S. Pat. No. 4,301,146. Other stabilizing agents include, but are not limited to, cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, microcrystalline cellulose and carboxymethylcellulose sodium; and vinyl polymers and

copolymers such as polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers. The stabilizing agent is present in an amount effective to provide the desired stabilizing effect; generally, this means that the ratio of cysteamine or cystamine to the stabilizing agent is at least about 1:500 w/w, more commonly about 1:99 w/w.

[0047] The tablets are manufactured by first enterically coating the cysteamine or cystamine. A method for forming tablets herein is by direct compression of the powders containing the enterically coated cysteamine or cystamine, optionally in combination with diluents, binders, lubricants, disintegrants, colorants, stabilizers or the like. As an alternative to direct compression, compressed tablets can be prepared using wet-granulation or dry-granulation processes. Tablets may also be molded rather than compressed, starting with a moist material containing a suitable water-soluble lubricant.

[0048] In an alternative embodiment, the enterically coated cysteamine or cystamine are granulated and the granulation is compressed into a tablet or filled into a capsule. Capsule materials may be either hard or soft, and are typically sealed, such as with gelatin bands or the like. Tablets and capsules for oral use will generally include one or more commonly used excipients as discussed herein.

[0049] For administration of the dosage form, i.e., the tablet or capsule comprising the enterically coated cysteamine or cystamine, a total weight in the range of approximately 100 mg to 1000 mg is used. The dosage form is orally administered to a patient suffering from a condition for which an cysteamine or cystamine would typically be indicated, including, but not limited to, cystinosis and

neurodegenerative diseases such as Huntington's, Alzheimer's and Parkinson's disease.

[0050] The compositions of the disclosure can be used in combination with other therapies useful for treating cystinosis and neurodegenerative diseases and disorders. For example, indomethacin therapy (Indocid® or Endol®) is an anti-inflammatory used to treat rheumatoid arthritis and lumbago, but it can be used to reduce water and electrolyte urine loss. In children with cystinosis, indomethacin reduces the urine volume and therefore liquid consumption by about 30%, sometimes by half. In most cases this is associated with an appetite improvement. Indomethacin treatment is generally followed for several years.

[0051] Other therapies can be combined with the methods and compositions of the disclosure to treat diseases and disorders that are attributed or result from cystinosis. Urinary phosphorus loss, for example, entails rickets, and it may be necessary to give a phosphorus supplement. Carnitine is lost in the urine and blood levels are low. Carnitine allows fat to be used by the muscles to provide energy. Hormone supplementation is sometimes necessary. Sometimes the thyroid gland will not produce enough thyroid hormones. This is given as thyroxin (drops or tablets). Insulin treatment is sometimes necessary if diabetes appears, when the pancreas does not produce enough insulin. These treatments have become rarely necessary in children whom are treated with cysteamine, since the treatment protects the thyroid and the pancreas. Some adolescent boys require a testosterone treatment if puberty is late. Growth hormone therapy may be indicated if growth is not sufficient despite a good hydro electrolytes balance. Accordingly, such therapies can be combined with the enterically coated cysteamine and cystamine compositions and methods of the disclosure.

[0052] The effectiveness of a method or composition of the disclosure can be assessed by measuring leukocyte cystine concentrations. Dosage adjustment and therapy can be made by a medical specialist depending upon, for example, the severity of cystenosis and/or the concentration of cystine. Additional therapies including the use of omeprazole (Prilosec®) can reduce these symptoms.

[0053] In addition, various prodrugs can be "activated" by use of the enterically coated cysteamine. Prodrugs are pharmacologically inert, they themselves do not work in the body, but once they have been absorbed, the prodrug decomposes. The prodrug approach has been used successfully in a number of therapeutic areas including antibiotics, antihistamines and ulcer treatments. The advantage of using prodrugs is that the active agent is chemically camouflaged and no active agent is released until the drug has passed out of the gut and into the cells of the body. For example, a number of produgs use S-S bonds. Weak reducing agents, such as cysteamine, reduce these bonds and release the drug. Accordingly, the compositions of the disclosure are useful in combination with pro-drugs for timed release of the drug. In this aspect, a pro-drug can be administered followed by administration of an enterically coated cysteamine compositions of the invention (at a desired time) to activate the pro-drug.

[0054] It is to be understood that while the invention has been described in conjunction with specific embodiments thereof, that the foregoing description as well as the examples which follow are intended to illustrate and not limit the scope of the invention.

EXAMPLES

[0055] **Subjects.** Children with cystinosis, ≥ 12 years old, and taking regular cysteamine bitartrate (Cystagon; Mylan, Morgantown, WV) were recruited to the study (Table I). Adult control patients were recruited locally. Patients with cystinosis had a mean leukocyte cystine level of less than 2.0 nmol half-cystine/mg protein over the past year. Cysteamine therapy was discontinued 2 days before admission, and acid suppressants, antibiotics, nonsteroidal anti-inflammatory drugs, pro-kinetic agents, and antihistamines were discontinued 2 weeks before admission. None of the patients had undergone kidney transplantation. Baseline chemistry, *Helicobacter pylori* serologic study, complete blood count, and urinalysis were performed.

Table I. Cystinosis patient data

Patient	Age (yrs.)	Sex	Weight (kg)	Cysteamine dose (mg)*	Serum creatinine (mg/dL)
1	16	Male	61.5	500	1.0
2	14	Male	39.4	406	1.2
3	13	Female	39.1	406	1.5
4	19	Female	38.1	406	1.4
5	13	Female	50.1	500	1.0
6	16	Male	58.7	500	3.1

* Dose of cysteamine base delivered into varying delivery sites

[0056] **Cysteamine bitartrate delivery.** Cysteamine was infused through a silicone rubber nasocenteric tube (Dentsleeve Pty Ltd, Australia), 3 mm in diameter and 4.5 meters long. The tube, specifically made for this study, had a tungsten-weighted tip, and immediately proximal to this was an inflatable balloon (5-mL capacity). Immediately proximal to the balloon was an infusion port (1 mm diameter) through which the drug was delivered. After an overnight fast (except for water), the dose of cysteamine bitartrate (10 mg/kg/dose of base, maximum of 500 mg) was dissolved in 10 mL of water and infused over 1 to 2 minutes. On day 1 of the study, the nasocenteric tube was inserted into the

stomach. By day 3 of the study the tube had passed into the proximal small intestine (SI) just distal to the ligament of Treitz (confirmed fluoroscopically). The balloon was then inflated, and peristalsis propelled the tube distally. Tube position within the cecum was confirmed fluoroscopically on day 5 (day 7 in 4 patients because of slow transit). If the tube had migrated too far, it was retracted into the desired location.

[0057]. **Serum gastrin, cysteamine and leukocyte cystine measurements.** After an overnight fast (except for water) blood samples were taken at baseline and at varying intervals after intraluminal delivery of cysteamine. Serum gastrin levels were then measured at 30, 60, 90, and 120 minutes and 3 and 4 hours; cysteamine levels were measured at 0, 5, 10, 20, 30, 45, 60, 75, 90, 105, 120, and 150 minutes and 3, 4, 6, 8, 10, 12, and 16 hours; leukocyte cystine levels were measured at 1, 2, 3, 4, 6, and 12 hours in patients with cystinosis only. Gastrin was measured in picograms/mL with the Diagnostic Products Corporation (Los Angeles, Calif) gastrin radioimmunoassay-kit. Leukocyte cystine levels were measured in nmol half-cystine per mg protein by the Cystine Determination Lab (La Jolla, Calif).

[0058] To measure plasma cysteamine, 100- μ L plasma samples were collected in heparinized vacutainers and spun in a centrifuge within 1 hour, and plasma was stored at -18° C. The concentration of cysteamine was measured by use of tandem mass spectroscopy (API 2000 LC/MS/MS; Applied Biosystems, Foster City, Calif). Cysteamine concentrations were calculated with a calibration curve that was prepared by spiking plasma with buffered cysteamine solutions, and quality control samples were analyzed with each batch.

[0059] **Statistical analysis.** Mixed model restricted maximum likelihood (REML) repeated measures analysis of

variance with subjects as a random effect was performed on the absolute leukocyte cystine levels, on the leukocyte cystine level changes from baseline, and on the "area over the curve" (AOC) for leukocyte cystine level changes from baseline after cysteamine administration for the subjects with cystinosis. AOC is computationally analogous to area under the curve, but it is applied when values are predominantly decreasing below baseline values. Large AOC values reflect large decreases, and a negative AOC reflects a net increase in value. Main effects for site of delivery, time after delivery, and the interaction between site and time were tested, except just the site effect was tested for AOCs. In the absence of significant interaction when a main effect was detected, Tukey's honestly significant difference test (HSD) was applied to identify where differences occurred within a 5% family wise error rate. The Tukey HSD procedure controls for overall significance level when performing all pairwise comparisons. An additional analysis was performed with plasma cysteamine C_{\max} added to the AOC model.

[0060] REML repeated measures analyses of variance with subjects as a random effect were also performed as described above on AUC and the C_{\max} over time for plasma cysteamine levels separately for the subjects with cystinosis and control subjects and with both subject groups combined. Differences between means for the 3 sites were tested, plus group and group x site interaction effects for the combined groups. If a site effect was detected, Tukey's HSD was applied to determine which sites differed from each other.

[0061] REML repeated measures analyses of variance were also performed as described above on gastrin levels. The analyses were performed on 2 versions of datasets: the full dataset and all data after omitting observations collected at 30 minutes (1 subject was missing a blood sample taken at

30 minutes after small intestinal cysteamine delivery). A 5% significance level was used without adjustment for all statistical testing.

[0062] Six patients with cystinosis, (3 male, 3 female) with a mean age of 15.2 years (range 13-19 years) were recruited into the study (Table I). Eight healthy adult control patients (6 male, 2 female) with a mean age of 23.2 years (range 19-28 years) were enrolled. None of the children with cystinosis had undergone kidney transplantation. All control subjects received 500 mg cysteamine base, whereas the mean dose for subjects with cystinosis was 453 mg (range 406-500 mg). All subjects had normal liver function test results. In all subjects the nasoenteric tube passed successfully from the stomach into the upper SI; however, it did not progress any further in 2 subjects with cystinosis. In 2 of the control subjects the tube only reached the mid-ileum but did, however, progress to the cecum in 8 subjects (4 control subjects, 4 with cystinosis). There were no reported adverse effects with the insertion or removal of the nasoenteric tube (Figure 1).

[0063] **Symptoms.** Only 2 patients (1 male, 1 female) with cystinosis reported regular GI symptoms before the study, and these had responded to acid-suppression therapy. The male subject had severe retching and emesis about 15 minutes after receiving intragastric cysteamine but did not have any symptoms when the drug was infused into the proximal small intestine. The female child with cystinosis had mild transient nausea after SI drug delivery only. No other symptoms were reported after any other cysteamine delivery in the children with cystinosis. There were no associated adverse events with tube placement or removal.

[0064] **Plasma cysteamine.** Among the subjects with cystinosis as measured by analysis of variance, the mean plasma cysteamine C_{max} and AUCs (of the concentration-time

gradient) differed by site of cysteamine delivery (both $P < .03$). Site (') refers to either patients with cystinosis or control subjects. For the plasma cysteamine AUCs, the means differed between the duodenal and both gastric and cecal sites of delivery (Tukey HSD global $P < .05$). Among control subjects, the mean AUC did not differ among delivery sites ($P > .4$), but mean C_{max} did ($P < .05$). For both cystinosis and control groups the mean C_{max} values differed only between the duodenum and cecum; mean C_{max} values after duodenal versus gastric or gastric versus cecal delivery were not statistically different (Tables II and III).

Table II. Mean plasma cysteamine C_{max} levels ($\mu\text{mol/L}$) and area under curve (AUC) measurements in cystinosis subjects, controls, and combined cystinosis and control subjects, after delivery of cysteamine into the stomach, small intestine, and cecum						
	C_{max} Cystinosis	AUC Cystinosis	C_{max} Control	AUC Control	C_{max} Combined	AUC Combined
Stomach	35.5 (20.5)	3006 (1112)	39.5 (16.4)	3613 (1384)	37.8 (17.6)	3353 (1267)
Small Intestine	55.8 (13.0)	4299 (1056)	51.1 (20.7)	3988 (1659)	53.2 (17.4)	4047 (1376)
Cecum	21.9 (13.1)	3002 (909)	23.1 (15.3)	2804 (1323)	22.5 (13.2)	2903 (1056)

The standard deviations are in parenthesis

Table III. Comparisons of mean plasma cysteamine C_{max} ($\mu\text{mol/L}$) and AUC measurements for combined cystinosis subjects and control subjects among delivery sites		
	AUC	C_{max}
P value*	<0.01	<0.01
Stomach vs SI	+	+
Stomach vs Cecum	-	-
SI vs Cecum	+	+

+ Significant difference using Tukey's HSD test ($\alpha = 0.05$)

- No significant difference

* ANOVA test for equality of three delivery sites

[0065] When data from the control subjects were combined with cystinosis subject data, there was both a group effect ($P < .05$) and a site effect ($P < .01$) for AUCs, with a significant difference between mean AUC levels for the duodenum versus both the stomach and cecum. C_{max} values differed among sites ($P < .01$) but not between groups ($P > .4$). Group (*) refers to site of intestinal delivery. C_{max}

differed between duodenum versus both stomach and cecum (Figure 2).

[0066] **Leukocyte cystine.** There were significant differences among the 3 sites of delivery for cystine levels ($P < .04$), changes from baseline values ($P < .0001$), and AOCs for changes from baseline ($P < .02$). A Tukey HSD test, which controls for multiple comparisons, showed that mean leukocyte cystine levels differed between the cecum and stomach sites, but that cecum versus duodenum and stomach versus duodenum produced similar mean values. When the absolute cystine levels or AOCs for changes from baseline levels were evaluated, the significant differences in sites were found between the duodenum and both the stomach and cecum, but not between stomach and cecum (Tukey HSD global $P < .05$) (Figure 3). Plasma cysteamine C_{max} and AUC contributed a statistical effect on AOC ($P < .001$ and $P < .02$, respectively), even after controlling for delivery site (Figure 4).

[0067] **Blood gastrin.** For the full gastrin dataset, there was a significant difference among the means for the different delivery sites ($P < 0.1$), with the cecum resulting in a lower mean from that of the stomach and small intestine. Both group * and site † significant effects were detected after omitting observations from 30 minutes after delivery ($P < .05$ and $P < .01$, respectively). The 30-minute observations were omitted because of a missing data set. For these observations, mean levels of gastrin after delivery in the cecum were different from those from both the duodenum and stomach, although the latter did not differ from each other. The 1 boy (14 years) who had severe GI symptoms after intragastric, but not enteric or cecal, cysteamine delivery had a rise in baseline gastrin from 70 pg/mL to 121 pg/mL at 30 minutes after gastric cysteamine. Within the control group, more than half of the baseline and post-cysteamine

gastrin levels remained undetectable (<25 pg/mL), and none of the control subjects had a significant rise in gastrin after cysteamine delivery into any site.

[0068] Patients with cystinosis are required to ingest oral cysteamine (Cystagon) every 6 hours, day and night. When taken regularly, cysteamine can deplete intracellular cystine by up to 90% (as measured in circulating white blood cells), and this has been shown to reduce the rate of progression to kidney failure/transplantation and also to obviate the need for thyroid replacement therapy. Unfortunately, because of the strict treatment regimen and the associated symptoms, nonadherence with cysteamine therapy remains a problem, particularly among adolescent and young adult patients. Certainly, by reducing the frequency of required cysteamine dosing adherence can be improved. The disclosure shows a strong statistical association between the maximum plasma concentration (C_{max}) of cysteamine and AOC measurements for leukocyte cystine ($P < .001$). A higher C_{max} is achieved after delivery of cysteamine into the small intestine than when infused into the stomach or colon; this may be due to improved absorption rate from the SI, greater surface area of the SI, or less cysteamine undergoing hepatic first pass elimination when absorbed rapidly through the small intestine. When data were combined for patients with cystinosis and control subjects, there was a statistical difference between duodenal versus both gastric and colonic delivery for plasma cysteamine C_{max} and AUC levels (both $P < .05$). The lack of similar statistical significance for the cystinosis group alone may simply reflect the small number of patients studied. Changes from baseline leukocyte cystine levels were statistically significant for absolute cystine levels and for AOC when cysteamine was infused into the duodenum compared with both stomach and colon. As shown in Figure 3, the leukocyte

cystine levels remained below pre-delivery levels for up to 12 hours after a single dose of cysteamine into the small intestine. This would suggest that effective absorption of cysteamine through the SI, by causing a higher C_{max} and AUC on the cysteamine concentration-time gradient, could lead to prolonged depletion of leukocyte cystine and possibly less frequent daily dosing. Another explanation would be that by achieving a high enough plasma cysteamine concentration, more drug reaches the lysosome (where cystine accumulates). In the lysosome the cysteamine reacts with cystine forming the mixed disulfide of cysteamine and cysteine. The mixed disulfide exits the lysosome presumably via the lysine carrier. In the cytosol the mixed disulfide can be reduced by its reaction with glutathione. The cysteine released can be used for protein or glutathione synthesis. The cysteamine released from the mixed disulfide reenters the lysosome where it can react with another cystine molecule. Thus 1 molecule of cysteamine may release many molecules of cystine from the lysosome. This study showed a dramatic decrease in leukocyte cystine within an hour of cysteamine delivery. In retrospect, the finding from this study was that the leukocyte cystine levels remained at the 1-hour level for 24 hours, and even at 48 hours after delivery the levels had not returned to the pre-cysteamine level.

[0069] Cysteamine is a potent gastric acid-secretagogue that has been used in laboratory animals to induce duodenal ulceration; studies in humans and animals have shown that cysteamine-induced gastric acid hypersecretion is most likely mediated through hypergastrinemia. In previous studies performed in children with cystinosis who suffered regular upper gastrointestinal symptoms, a single oral dose of cysteamine (11-23 mg/kg) was shown to cause hypergastrinemia and a 2-to 3-fold rise in gastric acid-hypersecretion. Symptoms suffered by these individuals

included abdominal pain, heartburn, nausea, vomiting, and anorexia. Interestingly, only 2 of 6 subjects with cystinosis (who were known to suffer regular cysteamine-induced GI symptoms) had increased gastrin levels and symptoms, including nausea, retching, and discomfort after intragastric cysteamine. Gastrin levels were only available after small intestinal administration in 1 of the 2 children and the levels remained the same as baseline. Neither child had symptoms after enteric cysteamine delivery. None of the other patients with cystinosis or control subjects had an increase in gastrin levels with cysteamine infused into any site. This would suggest that cysteamine-induced hypergastrinemia may arise as a local effect on the gastric antral-predominant G-cells only in susceptible individuals. In addition, plasma gastrin levels usually peaks after intragastric delivery within 30 minutes, whereas the plasma cysteamine levels peaked later.^{8,10} In 2 previous studies, children with cystinosis were shown to have a significant rise in plasma gastrin levels after receiving intragastric cysteamine; as part of these study's entry criteria all subjects did, however, suffer with regular GI symptoms. Data from this study would suggest that cysteamine does not cause hypergastrinemia, and therefore acid-hypersecretion, in all patients with cystinosis. Thus acid suppression therapy would not be recommended in patients with cystinosis without upper GI symptoms.

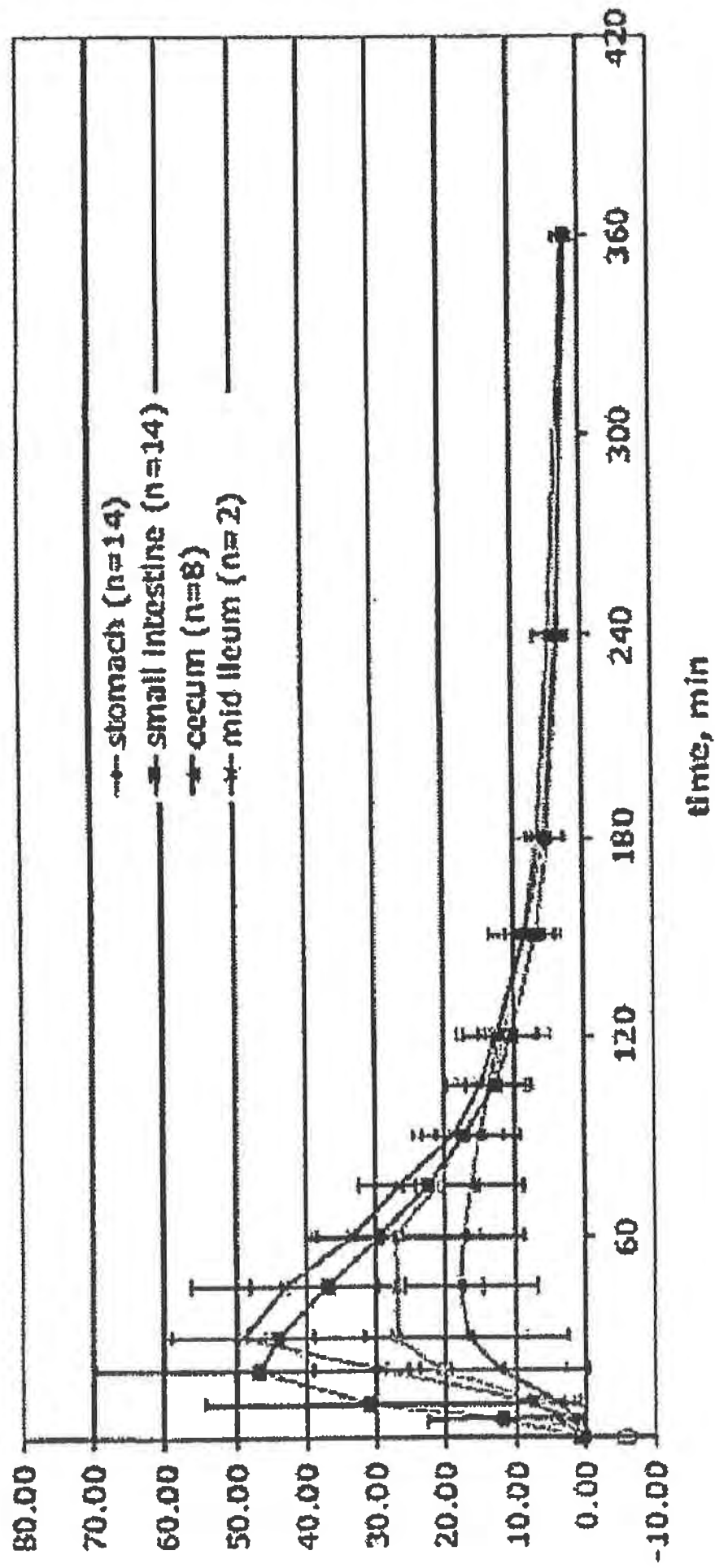
[0070] The data suggest that direct administration of cysteamine into the jejunum may result in prolonged leukocyte cystine depletion. In a previous study, a child who had a gastrojejunal feeding tube for oral feeding aversion and severe UGI symptoms, responded to intrajejunal cysteamine with a 3-fold rise in serum gastrin as compared with drug administration into the stomach. The leukocyte cystine response was not measured in this child. Therefore

patients with jejunal feeding tubes will have to be further evaluated.

[0071] Figures 5 and 6 shows results from a patient that remained on the twice daily EC-cysteamine for an extended period of time. Over this period the patient's leukocyte cystine levels have been measured regularly. The dose of twice daily EC-cysteamine is titrated against the patients symptoms and cystine levels. The patient's cystine levels have been 0.4, 1.0, 0.36.

[0072] This study provides data that may be used to improve the quality of life for patients with cystinosis. The present formulation of Cystagon comprises cysteamine in a capsule that will dissolve rapidly on contact with water, most likely within the stomach.

[0073] Although a number of embodiments and features have been described above, it will be understood by those skilled in the art that modifications and variations of the described embodiments and features may be made without departing from the teachings of the disclosure or the scope of the invention as defined by the appended claims.



THE EMBODIMENTS OF THE INVENTION FOR WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A composition comprising: an enterically coated cystamine or a pharmaceutically acceptable salt thereof, wherein the enteric coating provides increased delivery of cystamine to the small intestine.
2. The composition of claim 1, wherein the enteric coating of the enterically coated cystamine or pharmaceutically acceptable salt thereof releases the cystamine or pharmaceutically acceptable salt thereof when the composition reaches the small intestine or a region of the gastrointestinal tract of a subject in which the pH is greater than pH 4.5.
3. The composition of claim 1 or 2, wherein the enteric coating is selected from the group consisting of polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose propionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypopyl methylcellulose succinate, carboxymethyl ethylcellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers, typically formed from methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with copolymers of acrylic and methacrylic acid esters.
4. The composition of any one of claims 1 to 3, wherein the composition is formulated for oral administration.
5. The composition of any one of claims 1 to 4, wherein the composition further comprises a pharmaceutically acceptable carrier.
6. The composition of any one of claims 1 to 5, wherein the composition comprises a stabilizer.
7. A composition comprising: an enterically coated cysteamine bitartrate, wherein the enteric coating provides increased delivery of cysteamine to the small intestine.
8. The composition of claim 7, wherein the enteric coating of the enterically coated cysteamine bitartrate thereof releases the cysteamine bitartrate when the composition reaches the small intestine or a region of the gastrointestinal tract of a subject in which the pH is greater than pH 4.5.

9. The composition of claim 8, wherein the enteric coating is selected from the group consisting of polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose propionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypopyl methylcellulose succinate, carboxymethyl ethylcellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers, typically formed from methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with copolymers of acrylic and methacrylic acid esters.
10. The composition of any one of claims 7 to 9, wherein the composition is formulated for oral administration.
11. The composition of any one of claims 7 to 9, wherein the composition further comprises a pharmaceutically acceptable carrier.
12. The composition of any one of claims 1 to 11, wherein the composition comprises a stabilizer.
13. The composition of any one of claims 7 to 9, wherein the composition is formulated to provide a time to C_{max} of cysteamine bitartrate of between 2-4 hours.
14. Use of the composition of any one of claims 1 to 13 in the preparation of a medicament for treating a subject with cystinosis.
15. Use of the composition of any one of claims 1 to 13 for treatment of a subject with cystinosis.
16. Use of the composition of any one of claims 1 to 13 in the preparation of a medicament for treating a subject with a neurodegenerative disease or disorder.
17. Use of the composition of any one of claims 1 to 13 for treatment of a subject with a neurodegenerative disease or disorder.
18. A pharmaceutical formulation comprising the composition of claim 1 to 13 in a pharmaceutically acceptable carrier.
19. The use according to claim 15 or 17, further comprising use of a second therapeutic agent.

20. The use according to claim 15 or 17, wherein the frequency of said use is less than four times daily.
21. The use according to claim 15 or 17, wherein the frequency of said use is twice daily.
22. The use according to any one of claims 15, 17, 20 and 21, wherein the use comprises a total daily dose of 1.35 g/m^2 or less.
23. The use according to any one of claims 15, 17, 20, 21 and 22, wherein the use comprises a total daily dose of 0.5 to 1.0 g/m^2 or less.
24. The use of any one of claims 15, 17, 20, 21, 22 and 23, wherein said use provides a prolonged white blood cell cystine suppression with a 12 hour level below $1 \text{ nmol}/\frac{1}{2} \text{ cystine /mg protein}$.
25. The use of claims 15, 17, 20, 21, 22 and 23, wherein said use provides an increased AUC compared to a cysteamine or cystamine that is not enterically formulated.
26. The use of any one of claims 15, 17, 20, 21, 22 and 23, wherein the human is suffering from cystinosis or a neurodegenerative disease.
27. The use of claim 27, wherein the neurodegenerative disease is Huntington's Disease.
28. The use of any one of claims 15, 17, 20, 21, 22, 23, 24, 25, 26 and 27, wherein C_{max} is between 2-4 hours after use.
29. The use of claim 27, wherein the dose comprises cysteamine or cystamine at about 100 mg to about 1000 mg per dose.
30. The use according to any one of claims 14 to 17 and 19 to 29, wherein the pharmaceutical composition is a tablet or capsule.
31. The composition of any one of claims 1 to 13, wherein the enteric coating increases delivery of the cystamine or cysteamine to a region of the gastrointestinal tract of a subject in which the pH is between 4.5 and 6.5.
32. The composition of any one of claims 1 to 13, wherein the enteric coating increases delivery to the proximal or mid-small intestine or both.

33. The composition of any one of claims 1 to 13, wherein the enteric coating increase delivery to one or more of the duodenum, jejunum or mid-ileum.

34. The composition of any one of claims 1 to 13 and 31 to 33 wherein the composition is formulated for dosing less than four times per day.

35. A pharmaceutical composition comprising granules of enterically coated cysteamine bitartrate, wherein the enteric coating begins to dissolve at a pH of about 4.5 to about 5.5 and provides increased delivery of cysteamine bitartrate to the small intestine.

36. The pharmaceutical composition of claim 35, wherein the pharmaceutical composition is formulated to provide increased delivery of cysteamine bitartrate to the small intestine over a period of 2-3 hours

37. The pharmaceutical composition of claim 35 or 36, wherein the granules comprise a core of cysteamine bitartrate and a binder.

38. The pharmaceutical composition of claim 37, wherein the granules further comprise a filler selected from the group consisting of silicon dioxide, titanium oxide, alumina, talc, kaolin, powdered cellulose, and microcrystalline cellulose.

39. The pharmaceutical composition of claim 38, wherein the filler is microcrystalline cellulose.

40. The pharmaceutical composition of any one of claims 35 to 39, wherein the enteric coating is selected from the group consisting of polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose propionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypopyl methylcellulose succinate, carboxymethyl ethylcellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers, typically formed from methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with copolymers of acrylic and methacrylic acid esters.

41. The pharmaceutical composition of any one of claims 35 to 40, wherein the composition is formulated for oral administration.

42. A pharmaceutical composition comprising granules of enterically coated cystamine or pharmaceutically acceptable salt thereof, wherein the enteric coating begins to dissolve at a pH of about 4.5 to about 5.5 and provides increased delivery of cystamine or pharmaceutically acceptable salt thereof to the small intestine.
43. The pharmaceutical composition of claim 42, wherein the pharmaceutical composition is formulated to provide increased delivery of cystamine or pharmaceutically acceptable salt thereof to the small intestine over a period of 2-3 hours
44. The pharmaceutical composition of claim 42 or 43 wherein the granules comprise a core of cystamine or pharmaceutically acceptable salt thereof and a binder.
45. The pharmaceutical composition of claim 44, wherein the granules further comprise a filler selected from silicon dioxide, titanium oxide, alumina, talc, kaolin, powdered cellulose, and microcrystalline cellulose.
46. The pharmaceutical composition of claim 45, wherein the filler is microcrystalline cellulose.
47. The pharmaceutical composition of any one of claims 42 to 46, wherein the enteric coating is selected from the group consisting of polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose propionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypopyl methylcellulose succinate, carboxymethyl ethylcellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers, typically formed from methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with copolymers of acrylic and methacrylic acid esters.
48. The pharmaceutical composition of any one of claims 42 to 47, wherein the composition is formulated for oral administration.
49. A capsule comprising the pharmaceutical composition of any one of claims 35 to 48.
50. Use of the pharmaceutical composition of any one of claims 35 to 48 in the preparation of a medicament for treating a subject with cystinosis.

51. Use of the pharmaceutical composition of any one of claims 35 to 48 for treatment of a subject with cystinosis.
52. Use of the pharmaceutical composition of any one of claims 35 to 48 in the preparation of a medicament for treating a subject with a neurodegenerative disease or disorder.
53. Use of the pharmaceutical composition of any one of claims 35 to 48 for treatment of a subject with a neurodegenerative disease or disorder.
54. The use of claim 52 or 53, wherein the neurodegenerative disease is Huntington's Disease.
55. The use according to claim 51 or 53, further comprising use of a second therapeutic agent.
56. The use according to claim 51 or 53, wherein the frequency of said use is less than four times daily.
57. The use according to claim 51 or 53, wherein the frequency of said use is twice daily.
58. The use according to any one of claims 51, 53, 56 and 57, wherein the use comprises a total daily dose of 1.35 g/m^2 or less.
59. The use according to any one of claims 51, 53, 56 and 57, wherein the use comprises a total daily dose of 0.5 to 1.0 g/m^2 or less.
60. The use of any one of claims 51, 53, 56 and 57, wherein said use provides prolonged white blood cell cystine suppression with a 12 hour level below $1 \text{ nmol}/\frac{1}{2} \text{ cystine /mg protein}$.
61. The use of any one of claims 51, 53, 56 and 57, wherein said use provides an increased AUC compared to a cysteamine or cystamine that is not enterically formulated.
62. The use of any one of claims 51, 53, 56 and 57, wherein the human is suffering from cystinosis or a neurodegenerative disease.

63. The use of claim 62, wherein the neurodegenerative disease is Huntington's Disease.

64. The use of any one of claims 51, 53, 56 and 57, wherein C_{\max} is between 2-4 hours after use.

ATTACHMENT 4



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(54) Titre : PREPARATION DE BILLES DE CYSTEAMINE A LIBERATION RETARDEE

(54) Title: DELAYED RELEASE CYSTEAMINE BEAD FORMULATION, AND METHODS OF MAKING AND USING SAME

(57) Abrégé/Abstract:

An enteric-coated bead dosage form of cysteamine, and related methods of manufacture and use, are disclosed.

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DELAYED RELEASE CYSTEAMINE BEAD FORMULATION, AND METHODS OF MAKING AND USING SAME**[0001]****BACKGROUND****Field of the Disclosure**

[0002] The disclosure relates generally to delayed release formulations of cysteamine and pharmaceutically acceptable salts thereof, and related methods of making and treatment, e.g. treatment of cystinosis and other metabolic and neurodegenerative diseases including non-alcoholic fatty liver disease (NAFLD), Huntington's disease, Parkinson's disease, Rett Syndrome and others, use as free radical and radioprotectants, and as hepto-protectant agents. More particularly, the disclosure relates to enteric coated beads comprising cysteamine or a pharmaceutically acceptable salt thereof.

Brief Description of Related Technology

[0003] Cystinosis is a rare, autosomal recessive disease caused by intra-lysosomal accumulation of the amino acid cystine within various tissues, including the spleen, liver, lymph nodes, kidney, bone marrow, and eyes. Nephropathic cystinosis is associated with kidney failure that necessitates kidney transplantation. A specific treatment for nephropathic cystinosis is the sulfhydryl agent, cysteamine. Cysteamine has been shown to lower intracellular cystine levels, thereby reducing the rate of progression of kidney failure in children.

[0004] An enterically-coated cysteamine composition has been described, for increasing delivering of cysteamine to the small intestine and resulting in less frequent dosing compared to non enteric-coated cysteamine.

SUMMARY

[0005] One aspect of the disclosure provides a pharmaceutical dosage form including a plurality of cysteamine beads, the beads including a core particle including cysteamine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and an enteric membrane surrounding the core, wherein the plurality of beads is characterized by a distribution of particle sizes.

[0006] Another aspect of the disclosure provides a pharmaceutical dosage form including a plurality of cysteamine beads, the beads including a core particle including cysteamine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and an enteric membrane surrounding the core, wherein the plurality of beads is characterized by irregular bead shapes.

[0007] Yet another aspect of the disclosure provides a pharmaceutical dosage form including a plurality of cysteamine beads, the beads including a core particle including cysteamine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and an enteric membrane surrounding the core, wherein the plurality of beads is characterized by a distribution of enteric membrane thicknesses.

[0008] Still another aspect of the disclosure provides a method of making a pharmaceutical dosage form, including any embodiment described herein, by a method including coating a core particle including cysteamine or a pharmaceutically acceptable salt thereof and an excipient with an enteric polymer to form an enteric membrane. The method can include sorting core particles prior to enteric coating, to provide a selected core particle size distribution. The method can also include sorting enteric coated beads to provide a selected bead size distribution.

[0009] Yet another aspect of the disclosure provides a method for treating a patient in need of cysteamine comprising administering to the patient a dosage form described herein, including any embodiment described herein.

[0010] Still another aspect of the disclosure provides dosage forms and related methods according the disclosure herein wherein the primary active component is cystamine rather than cysteamine or a pharmaceutically acceptable salt thereof.

[0011] For the compositions and methods described herein, optional features, including but not limited to components, compositional ranges thereof, substituents, conditions, and steps, are contemplated to be selected from the various aspects, embodiments, and examples provided herein.

[0012] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. While the dosage form, method of making, and method of treatment are susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION

[0013] Described herein is pharmaceutical dosage form that includes a plurality of cysteamine beads, the beads including a core particle including cysteamine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and an enteric membrane surrounding the core particle. The plurality of beads can be characterized by a distribution of particle sizes. The plurality of beads can be characterized by irregular bead shapes. The plurality of beads can be characterized by a distribution of enteric membrane thicknesses. Also disclosed herein are a method for the preparation of the dosage form, including coating a core particle including cysteamine or a pharmaceutically acceptable salt thereof and an excipient with an enteric polymer to form the enteric membrane. Optionally, the core particle can be formed by a wet granulation method. Optionally, granules are sorted (e.g., via sieving) to a desired particle size range prior to enteric coating, and optionally again following enteric coating. Also disclosed herein are treatment methods including administering the dosage form to a patient in need thereof.

[0014] Cysteamine-containing, enteric-coated beads characterized by a distribution of particle sizes were shown to exhibit advantageous pharmacokinetics. Without intending to be bound by any particular theory, it is contemplated that the pharmacokinetics are influenced by the plurality of enteric-coated beads having a distribution of core particle sizes.

[0015] Cysteamine-containing, enteric-coated beads characterized by a irregular bead shapes were shown to exhibit advantageous pharmacokinetics. Without intending to be bound by any particular theory, it is contemplated that the pharmacokinetics are influenced by the plurality of enteric-coated beads having irregular bead shapes.

[0016] Cysteamine-containing, enteric-coated beads characterized by a distribution of enteric membrane thicknesses were shown to exhibit advantageous pharmacokinetics. Without intending to be bound by any particular theory, it is contemplated that the pharmacokinetics are influenced by the plurality of enteric-coated beads having a distribution of enteric membrane thicknesses.

[0017] In one aspect the distribution of enteric membrane thicknesses can be stated in terms of weight gain of enteric membrane material based on the total weight of the coated beads. Thus, in one embodiment, the distribution of enteric membrane thicknesses will be at least 2% based on the total weight of the coated beads. In another embodiment, the distribution of enteric membrane thicknesses will be at least 3%. In another embodiment, the distribution of enteric membrane thicknesses will be at least 4%. In another embodiment, the

distribution of enteric membrane thicknesses will be at least 5%. In another embodiment, the distribution of enteric membrane thicknesses will be at least 6%. In another embodiment, the distribution of enteric membrane thicknesses will be at least 7%. In another embodiment, the distribution of enteric membrane thicknesses will be at least 8% . In another embodiment, the distribution of enteric membrane thicknesses will be at least 9%. In another embodiment, the distribution of enteric membrane thicknesses will be at least 10%. In another embodiment, the distribution of enteric membrane thicknesses will be at least 11%. In another embodiment, the distribution of enteric membrane thicknesses will be at least 12%. In another embodiment, the distribution of enteric membrane thicknesses will be at least 13%. In another embodiment, the distribution of enteric membrane thicknesses will be at least 14%. For example, the difference in enteric membrane thickness from bead to bead can be in a range of +/- 1-7% based on the total weight of the coated beads. The distribution of enteric membrane thicknesses can be in a range of about 2% to about 14% based on the weight of the coated beads, or in a range of about 3% to about 13%, or in a range of about 4% to about 12%, or in a range of about 5% to about 11%, or in a range of about 6% to about 10%, or in a range of about 7% to 9%, or in a range of about 3% to 14%, or in a range of about 4% to 14%, or in a range of about 4% to 13%, or in a range of about 4% to about 12%, for example. In one embodiment, the absorption (AUC) of the dosage form when dosed orally is advantageously increased, compared to other dosage forms of cysteamine. Without intending to be bound by any particular theory, it is contemplated that the increase in absorption is influenced by the dosage form exhibiting a pseudo-extended release profile. The pseudo-extended release profile is contemplated to be influenced by one or more factors, including a distribution of enteric membrane thicknesses, a distribution of bead particle sizes, and the beads having irregular bead shapes. For example, in an embodiment wherein the beads have a distribution of enteric membrane thicknesses, it is contemplated that for beads which have a relatively thin coating, the coating will completely dissolve at the trigger pH relatively quickly to release the cysteamine composition, whereas for beads having a relatively thick coating the coating will take somewhat longer to completely dissolve and release the cysteamine composition. In another aspect, in an embodiment where the beads have a distribution of particle sizes and/or irregular bead shapes, it is contemplated that the gut transit time of the beads could be varied due to bead size and/or shape, such that the transit time until reaching the enteric membrane dissolution pH is varied, thus contributing to a pseudo-extended release profile. In another embodiment, the dosage form exhibits

substantially equivalent (e.g., bioequivalent) Cmax and/or AUC characteristics when administered orally inside a capsule shell or without a capsule shell.

[0018] The dosage form provides a progressive and predictable absorption curve. In one type of embodiment, the Tmax of the dosage form when dosed orally is advantageously more stable on a dose-to-dose basis, because the beads are individually enteric-coated. A predictable, consistent Tmax is highly advantageous for accomplishing a more consistent, sustained reduction of leukocyte cystine levels by use of cysteamine. For example, process-related variations in enteric membrane thickness or other influences on enteric membrane dissolution will affect only a fraction of the cysteamine in the dosage form and will tend to lead to the pseudo-extended release behavior described above. In contrast, enteric-coated capsules comprising cysteamine microspheres exhibited significant variability in absorption time from capsule to capsule.

[0019] In another embodiment, the dosage form exhibits advantageous storage stability, e.g. as measured by the amount of cystamine present following storage and/or by the total amount of related substances. The storage stability can be assessed following storage at typical ambient conditions (e.g. 25 °C and 40% relative humidity) or at accelerated stability conditions involving increased temperature and/or humidity.

[0020] The dosage form and methods are contemplated to include embodiments including any combination of one or more of the additional optional elements, features, and steps further described below (including those shown in the figures and Examples), unless stated otherwise.

[0021] In jurisdictions that forbid the patenting of methods that are practiced on the human body, the meaning of “administering” of a composition to a human subject shall be restricted to prescribing a controlled substance that a human subject will self-administer by any technique (e.g., orally, inhalation, topical application, injection, insertion, etc.). The broadest reasonable interpretation that is consistent with laws or regulations defining patentable subject matter is intended. In jurisdictions that do not forbid the patenting of methods that are practiced on the human body, the “administering” of compositions includes both methods practiced on the human body and also the foregoing activities.

[0022] As used herein, the term “comprising” indicates the potential inclusion of other agents, elements, steps, or features, in addition to those specified.

[0023] As used herein, the term wt.% is the weight percent based on the total weight, e.g. of the core particle, or enteric membrane, or total bead, as described in context. Unless stated

otherwise, the wt.% is intended to describe the weight percent based on dry weight (e.g., for a core particle following drying).

[0024] All ranges set forth herein include all possible subsets of ranges and any combinations of such subset ranges. By default, ranges are inclusive of the stated endpoints, unless stated otherwise. Where a range of values is provided, it is understood that each intervening value between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also contemplated to be part of the disclosure.

[0025] Unless expressly stated otherwise, all references to cysteamine herein are intended to encompass pharmaceutically-acceptable salts thereof, and for every reference to cysteamine herein the use of cysteamine bitartrate is specifically contemplated as an embodiment. As described in the Summary above, embodiments of the dosage forms and methods described herein can employ cystamine as the primary active component, rather than cysteamine or a pharmaceutically acceptable salt thereof.

[0026] Unless expressly stated otherwise, reference herein to a bead and properties thereof is intended to be interpreted as applying equally to a collection of beads (e.g., a plurality of such beads). Likewise, unless expressly stated otherwise, reference herein to a core particle and properties thereof is intended to be interpreted as applying equally to a collection of core particles (e.g., a plurality of such core particles).

[0027] As described above, a pharmaceutical dosage form is contemplated that includes a plurality of cysteamine beads, the beads including a core particle including cysteamine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and an enteric membrane surrounding the core particle, wherein the plurality of beads is characterized by a distribution of particle sizes.

[0028] In one embodiment, the particle sizes of the beads are in a range of about 0.7 mm to about 2.5 mm, or about 0.7 mm to about 2.8 mm, or about 0.8 mm to about 1.7 mm. For example, the target bead size can be up to 2.5 mm with no more than 10 percent variation over this size, to a maximum size of 2.8 mm.

[0029] As the particle size of the beads becomes too small, the variability in cysteamine content increases. As the particle size becomes too large, the beads are too large for use in

drug products that are labeled to be administered via sprinkling (e.g., on applesauce or other soft foods, such as jellies) and swallowed without chewing, or administered via an enteral feeding tube. Also as the particle size increases, it was found that the larger particles get coated more than the smaller particles, resulting in lower relative assay when compared to use of smaller particles. To compensate, relatively more such beads would be needed in order to meet the label strength per capsule, but because salts such as cysteamine bitartrate already have a high molecular weight, filling a capsule shell with sufficient large particles to meet the label strength per capsule becomes difficult or impossible (e.g. to fill a size 0 capsule to a 75mg strength of cysteamine free base). Accordingly the bead particle size in one type of embodiment is up to 1.7mm.

[0030] The distribution of bead particle sizes for various non-exclusive embodiments of the invention can be characterized in ways.

[0031] In one embodiment, the beads can be characterized by 5% or less of the beads by weight being retained on a #12 mesh (1.68mm) screen and 10% or less by weight passing through a #20 mesh (0.84mm) screen. In another embodiment, at least 80% by weight of the beads have a particle size in a range of about 850 μm to about 1180 μm , e.g. as determined by sieving.

[0032] The distribution of bead sizes can be characterized by a gradation test via analytical sieving. Thus, in another embodiment the distribution of bead sizes is characterized by 0% of the beads being retained on a 1700 μm sieve and less than 5% by weight of the beads being retained on a 1400 μm sieve. Optionally less than 30% by weight of the beads are retained on a 1180 μm sieve. Optionally less than 70% by weight of the beads are retained on a 1000 μm sieve. Optionally less than 20% by weight of the beads are retained on a 850 μm sieve. Optionally at least 15% by weight of the beads are retained on a 1180 μm sieve. Optionally at least 50% by weight of the beads are retained on a 1000 μm sieve. Optionally at least 10% by weight of the beads being retained on a 850 μm sieve.

[0033] Thus, for example, the distribution can be characterized by 0% of the beads being retained on a 1700 μm sieve and less than 5% by weight of the beads being retained on a 1400 μm sieve, and about 20% to about 30% by weight of the beads being retained on a 1180 μm sieve and then about 50% to about 70% (or about 55% to about 65%) by weight of the beads being retained on a 1000 μm sieve and then about 10% to about 20% by weight of the beads being retained on a 850 μm sieve.

[0034] In another embodiment, the distribution of bead sizes can be characterized by a median particle size in a range of about 850 μm to about 1180 μm .

[0035] The bead core particle can comprise one or more excipients. In one type of embodiment, the excipients can include one or more fillers, binders, and surfactants. Other optional ingredients can include, but are not limited to, glidants, lubricants, disintegrants, swelling agents, and antioxidants.

[0036] Fillers include, but are not limited to, lactose, saccharose, glucose, starch, microcrystalline cellulose, microfine cellulose, mannitol, sorbitol, calcium hydrogen phosphate, aluminum silicate, amorphous silica, and sodium chloride, starch, and dibasic calcium phosphate dehydrate. In one type of embodiment, the filler is not water soluble, although it may absorb water. In one type of embodiment, the filler is a spheronization aid. Spheronization aids can include one or more of crospovidone, carrageenan, chitosan, pectinic acid, glycerides, β -CD, cellulose derivatives, microcrystalline cellulose, powdered cellulose, polyplasdone crospovidone, and polyethylene oxide. In one embodiment, the filler includes microcrystalline cellulose.

[0037] Binders include, but are not limited to, cellulose ethers, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, propyl cellulose, hydroxypropyl cellulose, lower-substituted hydroxypropyl cellulose, hydroxypropylmethyl cellulose (hypromellose, e.g. hypromellose 2910, METHOCEL^{*} E), carboxymethyl cellulose, starch, pregelatinized starch, acacia, tragacanth, gelatine, polyvinyl pyrrolidone (povidone), cross-linked polyvinyl pyrrolidone, sodium alginate, microcrystalline cellulose, and lower-substituted hydroxypropyl cellulose. In one embodiment, the binders are selected from wet binders. In one type of embodiment, the binder is selected from cellulose ethers, e.g. hypromellose.

[0038] Surfactants include, but are not limited to, anionic surfactants, including sodium lauryl sulfate, sodium deoxycholate, dioctyl sodium sulfosuccinate, and sodium stearyl fumarate, nonionic surfactants, including polyoxyethylene ethers, and polysorbate 80, and cationic surfactants, including quaternary ammonium compounds. In one embodiment the surfactant is selected from anionic surfactants, e.g. sodium lauryl sulfate.

[0039] Disintegrants include, but are not limited to, starch, sodium cross-linked carboxymethyl cellulose, carmellose sodium, carmellose calcium, cross-linked polyvinyl pyrrolidone, and sodium starch glycolate, low-substituted hydroxypropyl cellulose, hydroxypropyl starch.

[0040] Glidants include, but are not limited to, polyethylene glycols of various molecular weights, magnesium stearate, calcium stearate, calcium silicate, fumed silicon dioxide, magnesium carbonate, magnesium lauryl sulfate, aluminum stearate, stearic acid, palmitic acid, cetanol, stearyl, and talc.

[0041] Lubricants include, but are not limited to, stearic acid, magnesium stearate, calcium stearate, aluminum stearate, and siliconized talc.

[0042] The amount of cysteamine free base in the core particle can be at least 10 wt.% or at least 15 wt.%, or at least 20 wt.%, or at least 25 wt.%, or at least 30 wt.%. For example, the amount of cysteamine bitartrate can be at least 50 wt.%, or at least 55 wt.%, or at least 60 wt.%, or at least 65 wt.%, or at least 70 wt.%, or at least 75 wt.%, or at least 80 wt.%, or at least 85 wt.% of the core particle, for example in a range of about 60 wt.% to about 90 wt.% or about 65 wt.% to about 85 wt.%. It is understood that any and all ranges including these values as endpoints is contemplated, for example, at least about 15 wt.% to about 90 wt.%, or at least about 20 wt.% to about 85 wt.%, or at least about 30 wt.% to about 85 wt.%, or at least about 50 wt.% to about 90 wt.%. As the dose of cysteamine free base can be up to about 2 g/m²/day, and the amount of free base is relatively small compared to the molecular weight of salts (e.g. the bitartrate salt) it is preferred that the core particle have as much active ingredient as possible while allowing the creation and processing of core particles.

[0043] The amount of filler in the core particle is not particularly limited. In embodiments, the amount of filler (e.g. microcrystalline cellulose) can be in a range of about 10 wt.% to about 30 wt.%, or about 16 wt.% to about 23 wt.%, or at least 19 wt.% or at least 19.5 wt.%, for example about 20 wt.%.

[0044] The amount of binder in the core particle is not particularly limited. In embodiments, the amount of binder (e.g. hypromellose) can be in a range of about 1 wt.% to about 10 wt.%, or about 2 wt.% to about 8 wt.%, or about 4 wt.% to about 6 wt.%, for example about 5 wt.%.

[0045] The amount of surfactant, e.g. as a processing aid, in the core particle is not particularly limited. In embodiments, the amount of surfactant (e.g. microcrystalline cellulose) can be in a range of about 0.1 wt.% to about 1 wt.%, or about 0.2 wt.% to about 0.8 wt.%, or about 0.4 wt.% to about 0.6 wt.%, for example about 0.5 wt.%.

[0046] The enteric (gastro-resistant) membrane material, e.g. polymer, can be one that will dissolve in intestinal juices at a pH level higher than that of the stomach, e.g. a pH of greater than 4.5, such as within the small intestine, and therefore permit release of the active

substance in the regions of the small intestine and substantially not in the upper portion of the GI tract. In one type of embodiment, the enteric material begins to dissolve in an aqueous solution at pH between about 4.5 to about 5.5. In another type of embodiment, the enteric material rapidly dissolves in an aqueous solution at pH between of about 5. In another type of embodiment, the enteric material rapidly dissolves in an aqueous solution at pH between of about 5.5.

[0047] For example, pH-sensitive materials will not undergo significant dissolution until the dosage form has emptied from the stomach. The pH of the small intestine gradually increases from about 4.5 to about 6.5 in the duodenal bulb to about 7.2 in the distal portions of the small intestine (ileum). In order to provide predictable dissolution corresponding to the small intestine transit time of about 3 hours (e.g., 2-3 hours) and permit reproducible release therein, the membrane should begin to dissolve within the pH range of the duodenum, and continue to dissolve at the pH range within the small intestine. Therefore, the amount (thickness) of enteric membrane should be sufficient to be substantially dissolved during the approximate three hour transit time within the small intestine (e.g., the proximal and mid-small intestine).

[0048] Enteric (gastro-resistant) materials can include, but are not limited to, one or more of the following: cross-linked polyvinyl pyrrolidone; non-cross linked polyvinylpyrrolidone; hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, cellulose acetate succinate; cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, cellulose acetate trimellitate; starch acetate phthalate; polyvinyl acetate phthalate; carboxymethyl cellulose; methyl cellulose phthalate; methyl cellulose succinate; methyl cellulose phthalate succinate; methyl cellulose phthalic acid half ester; ethyl cellulose succinate; carboxymethylamide; potassium methacrylatedivinylbenzene copolymer; polyvinylalcohols; polyoxyethyleneglycols; polyethylene glycol; sodium alginate; galactomannone; carboxypolymethylene; sodium carboxymethyl starch; copolymers of acrylic acid and/or methacrylic acid with a monomer selected from the following: methyl methacrylate, ethyl methacrylate, ethyl acrylate, butyl methacrylate, hexyl methacrylate, decyl methacrylate, lauryl methacrylate, phenyl methacrylate, methyl acrylate, isopropyl acrylate, isobutyl acrylate, or octadecyl acrylate, e.g. EUDRAGIT^{*}-L and -S series, including L 100-55, L 30 D-55, L 100, S 100, L 12.5, and S 12.5, available from Evonik Industries; polyvinyl acetate; fats; oils; waxes; fatty alcohols; shellac; zein; gluten; ethylacrylate-maleic acid anhydride copolymer; maleic acid anhydride-vinyl methyl ether copolymer; styrol-maleic acid copolymer; 2-ethyl-hexyl-acrylate maleic acid anhydride; crotonic acid-vinyl

acetate copolymer; glutaminic acid/glutamic acid ester copolymer; carboxymethylethylcellulose glycerol monoctanoate; polyarginine; poly(ethylene); poly(propylene); poly(ethylene oxide); poly(ethylene terephthalate); poly(vinyl isobutyl ether); poly(vinyl chloride); and polyurethane. A combination of enteric materials may also be used. In one embodiment, the enteric material rapidly dissolves at pH 5.5 and higher, to provide fast dissolution in the upper bowel. For example, the enteric material can be selected from a copolymer of methacrylic acid and methyl methacrylate, and a copolymer of methacrylic acid and ethyl acrylate. For example, an enteric polymer is poly(methacrylic acid co-ethyl acrylate)1:1 (EUDRAGIT L 30 D-55 and EUDRAGIT L100-55).

[0049] Examples of some enteric coatings are disclosed in U.S. Pat. No. 5,225,202, including beeswax and glyceryl monostearate; beeswax, shellac and cellulose; and cetyl alcohol, mastic and shellac, as well as shellac and stearic acid (U.S. Pat. No. 2,809,918); polyvinyl acetate and ethyl cellulose (U.S. Pat. No. 3,835,221); and neutral copolymer of polymethacrylic acid esters (Eudragit L30D) (F. W. Goodhart et al., Pharm. Tech., pp. 64-71, April 1984); copolymers of methacrylic acid and methacrylic acid methylester (Eudragits), or a neutral copolymer of polymethacrylic acid esters containing metallic stearates (Mehta et al., U.S. Pat. Nos. 4,728,512 and 4,794,001). Such coatings comprise mixtures of fats and fatty acids, shellac and shellac derivatives and the cellulose acid phthlates, e.g., those having a free carboxyl content. See also Remington's Pharmaceutical Sciences, A. Osol, ed., Mack Pub. Co., Easton, Pa. (16th ed. 1980) at pages 1590-1593, and Zeitova et al. (U.S. Pat. No. 4,432,966), for descriptions of suitable enteric coating compositions.

[0050] One or more plasticizers can be added to enteric polymers in order to increase their pliability and reduce brittleness, as it is known in the art. Suitable plasticizers are known in the art and include, for example, butyl citrates, triethyl citrate, diethyl phthalate, dibutyl sebacate, PEGs (e.g. PEG 6000), acetyl triethyl citrate, and triacetin. In one type of embodiment, the plasticizer is triethyl citrate. While some enteric materials are flexible and do not require addition of plasticizers, more brittle polymers (e.g., Eudragit L/S types, Eudragit RL/RS, and Eudragit FS 30 D) benefit from plasticizers, e.g. in the range of 5 wt.% to 30 wt.% based on the dry polymer mass, e.g. about 8 wt.% to about 12 wt.% triethyl citrate with poly(methacrylic acid co-ethyl acrylate)1:1.

[0051] One or more anti-tacking agents (antiadherents) can also be added to an enteric coating mixture in order to reduce the tackiness of the film and prevent agglomeration, as it is known in the art. Anti-tacking agents include talc, and glyceryl monostearate, fumed silica (e.g., AEROSIL^{*} 200), precipitated silica (e.g., SIPERNAT PQ), and magnesium stearate, for

example. Anti-tacking agents can be used in any suitable quantity, for example in a range of about 10 wt.% to 100 wt.% based on dry polymer mass, or about 10 wt.% to about 50 wt.%, or about 10 wt.% to about 30 wt. %, or about 15 wt.% to about 30 wt.%. For example, in one embodiment the amount of talc is in a range of 15 wt.% to about 30 wt.%, based on dry polymer mass.

[0052] One or more surfactants can also be added to an enteric coating mixture in order to improve substrate wettability and/or stabilize suspensions, as it is known in the art. Surfactants include Polysorbate 80, sorbitan monooleate, and sodium dodecyl sulfate, for example.

[0053] The enteric membrane can be formed by any suitable process. Coating processes include pan coating, fluid bed coating, and dry coating (e.g., heat dry coating and electrostatic dry coating), for example. Pan coating and fluid bed coating using solvent are well established processes. In liquid coating, the enteric material and optional excipients (e.g. pigments, plasticizers, anti-tacking agents) are mixed in an organic solvent or water to form a solution or dispersion. The coating solution or dispersion is sprayed into solid dosage forms in a pan coater or a fluid bed dryer and dried by hot air. For example, in a Wurster fluid bed coating process, the coating fluid is sprayed from the bottom of the fluid bed apparatus, whereas in an alternative the coating fluid is applied by top spraying, and in another alternative tangential spray is applied.

[0054] The amount of enteric material applied is sufficient to achieve desired acid resistance and release characteristics. For example, in one embodiment the amount of enteric membrane will be sufficient to meet United States Pharmacopeia (USP) <711> requirements (USP 36-NF 31) for delayed-release dosage forms, thereby not releasing 10.0 wt.% of drug after 2 hours in 0.1N HCl. In another aspect, the formulation will be sufficient to release at least 80% of the active in 20 minutes in pH 6.8 buffer solution, e.g. using the dissolution method of USP 36-NF 31 section <711>.

[0055] In one type of embodiment, the enteric membrane is present in an amount in a range of about 20% to 40%, or 25% to about 35% as measured by the weight gain compared to the uncoated particle cores, or in a range of about 25% to about 31% weight gain, or about 27% to about 31% weight gain, or about 28.5% to about 31% weight gain, based on the weight of the uncoated particle cores.

[0056] The beads with enteric membrane can be sorted (e.g., via sieving) to a desired particle size. In embodiments, the particle size range can be any particle size range or

combination thereof described above in connection with the core particles. In one type of embodiment, the particle size range will be the same as the particle size range of the uncoated core particles. For example, the beads can be sieved such that 5% or less of the bead core particles by weight are retained on a #12 mesh (1.68mm) screen and 10% or less by weight pass through a #20 mesh (0.84mm) screen.

[0057] Additional lubricant (glidant, anti-tack agent) can be added to the coated beads in powder form. Anti-tacking agents include talc, glyceryl monostearate, fumed silica (e.g., AEROSIL 200), and precipitated silica (e.g., SIPERNAT PQ), for example. For example talc powder can be added to the coated beads, for example in an amount of 0.1 wt.% to about 1 wt.% based on the total bead weight.

[0058] The formulation can include a capsule shell in which the beads are disposed. Soft and hard capsule shells are known. In one embodiment, the capsule shell is a hard capsule shell, e.g. a gelatin capsule shell or a vegetable-based hard capsule shell.

[0059] Thus, for example, one type of embodiment combining various of the features described above includes a pharmaceutical dosage form including a plurality of cysteamine beads, the beads including a core particle comprising cysteamine bitartrate, a filler (optionally microcrystalline cellulose), a binder (optionally hypromellose), and an enteric membrane (optionally Eudragit L30 D-55) surrounding the core, wherein the plurality of beads is characterized by a distribution of particle sizes in a range of about 0.7 mm to about 2.5 mm, wherein the enteric membrane is present in an amount in a range of about 20% to about 40% based on the weight of the bead core particles, and wherein the beads are disposed in a capsule shell.

[0060] Pharmacokinetics

[0061] As mentioned above, the dosage form can advantageously be designed have one or more pharmacokinetic characteristics, e.g. in humans.

[0062] In one embodiment, the pharmaceutical dosage form is characterized by a mean T_{max} upon oral dosing, fasted, of greater than 75 minutes, or at least 110 minutes, or at least 2 hours, or at least 3 hours, or in a range of about 2.2 hours to about 3.48 hours, or about 2.22 hours to about 3.34 hours, or about 2.78 hours, or a T_{max} in a range of 80% to 125%, or 80% to 120% of such reference T_{max} .

[0063] In another embodiment, the pharmaceutical dosage form is characterized by a mean C_{max} upon oral dosing, fasted, in a range of about 22.16 $\mu\text{mol/L}$ to about 34.63 $\mu\text{mol/L}$, or

about 22.16 $\mu\text{mol/L}$ to about 33.24 $\mu\text{mol/L}$, or about 22.7 $\mu\text{mol/L}$, normalized to a 450mg dose, or a C_{max} in a range of 80% to 125%, or 80% to 120% of such reference C_{max} . In another embodiment, the pharmaceutical dosage form is characterized by a mean $C_{\text{max_D}}$ upon oral dosing in a range of about 0.004 to about 0.006 mg/L/mg.

[0064] In another embodiment, the pharmaceutical dosage form is characterized by a mean AUC (0-6 hours) upon oral dosing, fasted, in a range of about 60.74 $\mu\text{mol}\cdot\text{h/L}$ to about 94.91 $\mu\text{mol}\cdot\text{h/L}$, or about 60.74 $\mu\text{mol}\cdot\text{h/L}$ to about 91.12 $\mu\text{mol}\cdot\text{h/L}$, or about 75.93 $\mu\text{mol}\cdot\text{h/L}$, normalized to a 450 mg dose, or a bioequivalent AUC (0-6 hours) in a range of 80% to 125%, or 80% to 120% of such reference AUC (0-6 hours). In another embodiment, the pharmaceutical dosage form is characterized by a mean AUC (0-12 hours) upon oral dosing in a range of about 79.41 $\mu\text{mol}\cdot\text{h/L}$ to about 124.08 $\mu\text{mol}\cdot\text{h/L}$, or about 79.41 $\mu\text{mol}\cdot\text{h/L}$ to about 119.11 $\mu\text{mol}\cdot\text{h/L}$, or about 99.26 $\mu\text{mol}\cdot\text{h/L}$, normalized to a 450 mg dose, or a bioequivalent AUC (0-12 hours) in a range of 80% to 125%, or 80% to 120% of such reference AUC (0-12 hours). In another embodiment, the pharmaceutical dosage form is characterized by a mean AUC (0-inf_D) upon oral dosing in a range of about 0.86 min $\cdot\text{mg/L/mg}$ to about 1.35 min $\cdot\text{mg/L/mg}$, or about 0.86 min $\cdot\text{mg/L/mg}$ to about 1.3 min $\cdot\text{mg/L/mg}$, or a bioequivalent AUC (0-inf_D) in a range of 80% to 125%, or 80% to 120% of such reference AUC (0-inf_D).

[0065] In example embodiments, any of the described pharmaceutical dosage forms can be characterized by providing mean pharmacokinetic parameters upon oral dosing, fasted, of: T_{max} 183 \pm 90 minutes, C_{max} 3.5 \pm 1.7 mg/L, and/or AUC (0-inf_D) 1.08 \pm 0.46 min $\cdot\text{mg/L/mg}$, or a bioequivalent T_{max} , C_{max} or AUC in a range of 80% to 125%, or 80% to 120% of such reference parameter.

[0066] In example embodiments, any of the described pharmaceutical dosage forms can be characterized by providing mean pharmacokinetic parameters upon oral dosing of the whole capsule, fasted, of: T_{max} 194 \pm 38 minutes, C_{max} 2.3 \pm 0 mg/L, and/or AUC (0-inf_D) 0.84 \pm 0.19 min $\cdot\text{mg/L/mg}$, or a bioequivalent T_{max} , C_{max} or AUC in a range of 80% to 125%, or 80% to 120% of such reference parameter; and/or mean pharmacokinetic parameters upon oral dosing of the beads, sprinkled on applesauce, of: T_{max} 190 \pm 61 minutes, C_{max} 2.3 \pm 0.7 mg/L, and/or AUC (0-inf_D) 0.85 \pm 0.21 min $\cdot\text{mg/L/mg}$, or a bioequivalent T_{max} , C_{max} or AUC in a range of 80% to 125%, or 80% to 120% of such reference parameter.

[0067] In another embodiment, the pharmaceutical dosage form is characterized by being bioequivalent when administered orally, fasted, in a hard capsule shell compared to the beads

being administered orally, fasted, without a capsule shell. For example, the pharmaceutical dosage form can be characterized by the dosage form when administered orally in a hard capsule shell exhibiting a C_{max} in a range of 80% to 125%, or 80% to 120%, of C_{max} exhibited by the beads administered orally without a capsule shell. In another embodiment, the dosage form can be characterized by the dosage form when administered orally in a hard capsule shell exhibiting an AUC (0-12h) or AUC (0-inf) in a range of 80% to 125%, or 80% to 120%, of that exhibited by the beads administered orally without a capsule shell, respectively. In one embodiment, both the C_{max} and the AUC are within the tolerance ranges just described.

[0068] Purity

[0069] In one type of embodiment, the dosage form is characterized by having less than 5 wt.% cystamine, based on the amount of cysteamine, as determined by reverse phase HPLC with UV detection, as described herein. In other embodiments, the dosage form is characterized by having less than 5 wt.% cystamine, based on the amount of cysteamine, following 12 months storage at 25 °C and 40% relative humidity (RH), optionally as determined by reverse phase HPLC with UV detection, as described herein. In another type of embodiment, the dosage form is characterized by having less than 5 wt.% cystamine, based on the amount of cysteamine, following 18 months storage at 25 °C and 40% RH optionally as determined by reverse phase HPLC with UV detection, as described herein. In another type of embodiment, the dosage form is characterized by having less than 5 wt.% cystamine, based on the amount of cysteamine, following 24 months storage at 25 °C and 40% RH optionally as determined by reverse phase HPLC with UV detection, as described herein. In another type of embodiment, the dosage form is characterized by having less than 5 wt.% cystamine, based on the amount of cysteamine, following 30 months storage, or more, at 25 °C and 40% RH optionally as determined by reverse phase HPLC with UV detection, as described herein. Examples of suitable reverse phase HPLC assays are described herein.

[0070] In another type of embodiment, the dosage form is characterized by having less than 5 wt.% cystamine, based on the amount of cysteamine, following 12 months storage at 25 °C and 60% RH, optionally as determined by reverse phase HPLC with UV detection, as described herein. In another type of embodiment, the dosage form is characterized by having less than 5 wt.% cystamine, based on the amount of cysteamine, following 18 months storage at 25 °C and 60% RH, optionally as determined by reverse phase HPLC with UV detection, as described herein. In another type of embodiment, the dosage form is characterized by having less than 5 wt.% cystamine, based on the amount of cysteamine, following 24 months

storage, or more, at 25 °C and 60% RH, optionally as determined by reverse phase HPLC with UV detection, as described herein.

[0071] In another type of embodiment, the dosage form is characterized by having less than 5 wt.% cystamine, based on the amount of cysteamine, following 3 months storage at 40 °C and 75% RH, optionally as determined by reverse phase HPLC with UV detection, as described herein. In another type of embodiment, the dosage form is characterized by having less than 5 wt.% cystamine, based on the amount of cysteamine, following 6 months storage at 40 °C and 75% RH, optionally as determined by reverse phase HPLC with UV detection, as described herein.

[0072] Any of the foregoing embodiments can be further characterized by having less than 8 wt.% total related substances (impurities) based on the amount of cysteamine, under the described storage conditions and times based on reverse phase HPLC with UV detection, as described herein.

[0073] Method of making

[0074] Also contemplated is a method for the preparation of a dosage form according to the disclosure here, including coating a core particle comprising cysteamine or a pharmaceutically acceptable salt thereof and an excipient with an enteric polymer to form the enteric membrane.

[0075] The core particle including cysteamine or a pharmaceutically acceptable salt thereof can be formed by any suitable process. In one embodiment, the core particle is formed by granulating a mixture of cysteamine or a pharmaceutically acceptable salt thereof with an excipient and milling to a desired particle size range. In another embodiment, the core particle can be formed by extrusion and spheronization of a mixture of cysteamine or a pharmaceutically acceptable salt thereof with an excipient. Granulating processes can include fluid bed granulation, wet granulation, hot melt granulation, and spray congealing, for example. Other processes include slugging and roller compaction. As it is known in the art, the mixtures which are to be granulated can first be dry-blended. The dry-blended dry ingredients can be mixed with water, prior to extrusion.

[0076] It has been found that extrusion and spheronization of a mixture of cysteamine or a pharmaceutically acceptable salt thereof with an excipient can provide desirable core particles with a distribution of particle sizes as described herein and one or more other desirable properties. Cysteamine bitartrate oxidizes in air and in water, and with heat. Thus, short processing times can lead to a more stable product. For example, reducing the amount of

spheronization reduces the amount of friction and related heat. For example, reducing the amount of time that the product is exposed to air (either in the moist state and/or before packaging) also reduces the amount of oxidation. On the other hand, rapid processing by extrusion and spheronization can lead to a poor quality product, for example in having a large fraction of the pellet cores falling outside a desired particle size range. The amount of moisture absorbed by spheronization aids (which does not happen immediately, but instead over time) influences the spheronization characteristics of the beads. Accordingly, it was determined that the moisture content of the wet mass, the related wet hold time for swelling of spheronization aid(s), and the spheronization time are parameters that can be optimized to achieve both good product yield, for example in a particle size range described herein, while maintaining good stability, e.g. not more than 5 wt.% cystamine based on the amount of cysteamine, as described herein.

[0077] Accordingly, in one embodiment the moisture content of the granulation mixture, prior to drying, is in a range of about 20 wt.% to about 40 wt.%, or 25 wt.% to about 35 wt.%, or about 28 wt.% to about 32 wt.%, or at least about 28 wt.%, or at least about 28.5, or at least about 20 wt.% to about 40 wt.%, or at least about 25 wt.% to about 35 wt.%, or at least about 27 wt.% to about 31 wt.% or at least about 28.5 wt.% to about 31 wt.%.

[0078] The wet mass can be held for a period of time prior to extrusion, e.g. in order to allow the spheronization aid to swell with granulating fluid. The hold time can be at least 15 minutes, at least 30 minutes, at least 45 minutes, or at least 60 minutes, for example. The hold time can be in a range of about 15 minutes to about 120 minutes, or about 30 minutes to 100 minutes, or 60 minutes to 90 minutes, for example.

[0079] As described above in connection with description of the core particles, the method can include a step of sorting (e.g., by sieving) the core particles prior to enteric coating, to retain particles in a predetermined size range, for example sizes in a range of about 0.7 mm to about 2.8 mm, or about 0.7 mm to about 2.5 mm, or about 0.8 mm to about 1.7 mm, or any range described above in connection with the core particles.

[0080] As described above in connection with description of the beads, the method can include a step of sorting (e.g., by sieving) the beads after enteric coating, to retain particles in a predetermined size range, for example sizes in a range of about 0.7 mm to about 2.8 mm, or about 0.7 mm to about 2.5 mm, or about 0.8 mm to about 1.7 mm, or any range described above in connection with the core particles.

[0081] In an extrusion and spheronization process, the following optional features can be employed, individually or in one or more combinations thereof. Water can be used as a granulation agent. Microcrystalline cellulose can be used in the core particles as a spheronization aid. Hypromellose can be included in the core particles as a binder. The extrusion screen size can be 1.0mm. The friction plate of the spheronizer can be cross-hatched. The friction plate of the spheronizer can be cross-hatched with a square pitch of at least 3mm, or greater than 3 mm, or at least 4mm, or greater than 4mm, or in a range of about 3 mm to about 7 mm, or about 5 mm. The spheronization time can be less than about 5 minutes, or less than about 4 minutes, or less than about 3 minutes, or less than about 2 minutes, or up to 1 minute. The spheronized particles can include non-spherical particles (i.e. irregular shapes), e.g. a substantial fraction thereof, e.g. at least 20 wt.% or at least 30 wt.%, or at least 40 wt.% or at least 50 wt.% or at least 60 wt.%, or at least 70 wt.% thereof.

[0082] The beads and/or filled capsules can be stored with a desiccant. The beads and/or filled capsules can be stored with an oxygen absorber.

[0083] For example, one embodiment of the method combining various of the parameters described above includes a method for the preparation of a pharmaceutical dosage form including cysteamine beads, including forming a wet mass comprising cysteamine bitartrate and an excipient, optionally microcrystalline cellulose, with a moisture content in a range of in a range of about 20 wt.% to about 40 wt.%, extruding and spheronizing the wet mass including cysteamine bitartrate and excipient to make core particles, sorting the core particles to a target particle size range, optionally 0.7 mm to 2.5 mm, coating the sorted core particles with an enteric polymer to form including beads comprising a core particle and an enteric membrane, and sorting the bead particles to a target particle size range, optionally 0.7 mm to 2.5 mm.

[0084] Use / Administration

[0085] For administration of the dosage form, a total weight in the range of approximately 100 mg to 1000 mg (based on the free base) can be used. The dosage form can be orally administered to a patient suffering from a condition for which a cysteamine is indicated, including, but not limited to, cystinosis and other metabolic and neurodegenerative diseases including non-alcoholic fatty liver disease (NAFLD), Huntingon's disease, Parkinson's disease, Rett Syndrome and others, use as free radical and radioprotectants, and as hepto-protectant agents. In any method described herein, the treatment of humans is contemplated. The compositions of the disclosure can be used in combination with other therapies useful for

treating cystinosis and neurodegenerative diseases and disorders. For example, indomethacin therapy (Indocid® or Endol®) is an anti-inflammatory used to treat rheumatoid arthritis and lumbago, but it can be used to reduce water and electrolyte urine loss. In children with cystinosis, indomethacin reduces the urine volume and therefore liquid consumption by about 30%, sometimes by half. In most cases this is associated with an appetite improvement. Indomethacin treatment is generally followed for several years.

[0086] Other therapies can be combined with the methods and compositions of the disclosure to treat diseases and disorders that are attributed or result from cystinosis. Urinary phosphorus loss, for example, entails rickets, and it may be necessary to give a phosphorus supplement. Carnitine is lost in the urine and blood levels are low. Carnitine allows fat to be used by the muscles to provide energy. Hormone supplementation is sometimes necessary. Sometimes the thyroid gland will not produce enough thyroid hormones. This is given as thyroxin (drops or tablets). Insulin treatment is sometimes necessary if diabetes appears, when the pancreas does not produce enough insulin. These treatments have become rarely necessary in children whom are treated with cysteamine, since the treatment protects the thyroid and the pancreas. Some adolescent boys require a testosterone treatment if puberty is late. Growth hormone therapy may be indicated if growth is not sufficient despite a good hydro electrolytes balance. Accordingly, such therapies can be combined with the compositions and methods disclosed herein.

[0087] The effectiveness of a method or composition of the disclosure can be assessed by measuring leukocyte cystine concentrations. Dosage adjustment and therapy can be made by a medical specialist depending upon, for example, the concentration of cystine in leukocytes and the ability to tolerate the drug. Additional therapies including the use of omeprazole (Prilosec®) can reduce side effects of cysteamine administration, such as abdominal pain, heartburn, nausea, vomiting, and anorexia, which can result from cysteamine-induced gastric acid hypersecretion, for example.

[0088] In addition, various prodrugs can be “activated” by use of the enterically coated cysteamine. Prodrugs are pharmacologically inert, they themselves do not work in the body, but once they have been absorbed, the prodrug decomposes. The prodrug approach has been used successfully in a number of therapeutic areas including antibiotics, antihistamines and ulcer treatments. The advantage of using prodrugs is that the active agent is chemically camouflaged and no active agent is released until the drug has passed out of the gut and into the cells of the body. For example, a number of prodrugs use S—S bonds. Weak reducing agents, such as cysteamine, reduce these bonds and release the drug. Accordingly, the

compositions of the disclosure are useful in combination with pro-drugs for timed release of the drug. In this aspect, a pro-drug can be administered followed by administration of an enterically coated cysteamine composition of the invention (at a desired time) to activate the pro-drug.

EXAMPLES

[0089] The following examples are provided for illustration and are not intended to limit the scope of the invention.

Example 1 – Bead Production

[0090] Cysteamine bitartrate and excipients (microcrystalline cellulose, hypromellose, sodium lauryl sulfate) were milled through a Comil equipped with a 0.094" (2.3876 mm) screen operating at 500 RPM. The amount of each ingredient (per 75mg cysteamine capsule) is cysteamine bitartrate 258mg +/- 37.0 mg; microcrystalline cellulose 67.1mg +/- 9.6 mg; hypromellose 17.2mg +/- 2.5 mg; and sodium lauryl sulfate 1.75 mg +/- 0.25 mg. Cysteamine bitartrate was passed through the Comil first followed by the excipients (hypromellose 2910-5, sodium lauryl sulfate, and microcrystalline cellulose). Cysteamine bitartrate and the excipients were dry blended for approximately 15 minutes. While mixing at a setpoint speed of 47 rpm, purified water was slowly added (addition in approximately 4 minutes) into the blended components. After the water addition, the wet blend was mixed for an additional minute for a total of 5 minutes.

[0091] A sample of the wet blend was collected and moisture content was determined by loss on drying (LOD). The wet mass was discharged in polyethylene lined fiber drums and held for 60-90 minutes prior to extrusion/spheronization.

[0092] The granulated wet mass was loaded onto a NICA extruder equipped with a 1.0 mm screen at a feeder speed of 100 RPM setpoint and extruded at a setpoint speed of 55 RPM (50-60 RPM). The extruded product was immediately spheronized using a NICA Spheronizer equipped with 5.0 mm cross-hatched friction plates. Spheronization was performed at a target speed of 625 RPM (500-700 RPM) for 40-60 seconds. The particles were collected in double polyethylene lined fiber drums and stored at room temperature for further processing.

[0093] The wet particles were dried in a Niro fluid bed dryer with an inlet air temperature setpoint of 70°C (60-80°C). Drying was complete when the moisture content of uncrushed particles reached $\leq 1.0\%$ w/w by LOD. Sampling of the particles began when the outlet air temperature reached approximately 50°C and continued until the acceptance criterion of

≤1.0%. The dried particles were transferred to fiber drums lined with double polyethylene bags and stored at room temperature.

[0094] The dried particles were screened through a #12 mesh screen and a #20 mesh screen. Particles passing through the #12 mesh and retained on the #20 mesh were collected as product in double polyethylene lined containers with desiccant and oxygen absorber packets in the outer liner. The collected product may be re-passed through the screens as needed. Particles greater than #12 mesh and less than #20 mesh were not retained as product for coating.

[0095] An enteric coating solution of Eudragit L30 D-55, triethyl citrate, and talc in purified water was prepared in a mixing tank equipped with a propeller mixer and placed on a balance. Eudragit L 30 D-55 was added to the portable mixing tank through a 60-mesh screen. The final solution was mixed for a minimum of 30 minutes and mixed continuously during the coating process. Based on a 75mg cysteamine capsule, the amounts of coating ingredients were: Eudragit L30 D-55 66.2 mg +/- 9.5 mg; triethyl citrate 6.65 mg +/- 0.95 mg; talc 15.3 mg +/- 2.2 mg.

[0096] Spray lines connecting the portable mixing tank to the Niro fluid bed dryer were primed. The floor balance was tared prior to starting the coating process. The amount of coating solution sprayed was calculated as the amount required to increase the core particle weight by 25%.

[0097] The core particles were loaded into the Niro fluid bed dryer equipped with a Precision Coater which sprays from the bottom, 1.0 mm Nozzle, 30 mm Swirl Accelerator, and 300µm Filter Bonnet. The coating process parameters are provided in the table below.

Parameter	Setpoint	Range
Inlet Air Volume	450 scfm	300-600 scfm
Inlet Air Temperature	60°C	45 - 75°C
Product Temperature	30°C	25 - 45°C
Solution Spray Rate	0.220 kg/minute	0.200 – 0.240 kg/minute
Atomization Air Pressure	36 psi	32-40 psi

[0098] Once the target weight of coating solution was applied (25% of dry particle weight), the beads were weighed to confirm weight increase of ≥25.0%. If the weight was not ≥25.0% of the uncoated particle weight, the coating process was continued until ≥25.0% was achieved.

[0099] The coated beads were dried at an inlet temperature setpoint of 45°C (35 - 55°C) and inlet air volume setpoint of 350 scfm (300-400 scfm) until the LOD of the coated beads was $\leq 2.0\%$ w/w. Once the LOD was reached, the inlet air heating was turned off and the beads were circulated at an air inlet volume of 300-400 scfm until the product temperature reached not more than (NMT) 30°C.

[0100] The weight gain of the dried coated beads was calculated to confirm a maximum weight gain of $\leq 31.0\%$ was achieved. Visual inspection confirmed that the enteric membrane thickness was not consistent bead-to-bead, but instead there was a distribution of enteric membrane thicknesses.

[0101] The dried coated beads were screened through a #12 mesh and a #20 mesh screen in sequence. Beads passing through the #12 mesh screen and retained on the #20 mesh screen were collected as product in double polyethylene lined fiber drums with a desiccant and oxygen absorber canister in the outer liner. Mesh analysis testing can be performed as an in-process test to confirm the beads are within the limits of: NMT 5% are retained on a #12 mesh screen (1.68 mm) and NMT 10% pass through a #20 mesh screen (0.84 mm). If results are not within the limits, the product can be sorted by rescreening until the mesh analysis results meet the specified limits.

[0102] The dried coated beads were lubricated with talc prior to encapsulation. The coated beads were loaded in a V- blender; talc powder was added to the coated beads (calculated as 0.5% w/w of the total coated bead weight). The contents were mixed for a minimum of five minutes. The lubricated coated beads were transferred to double polyethylene lined fiber drums with desiccant and oxygen absorber packets in the outer liner and stored at room temperature. Lubricated coated beads were used in the manufacture of 75 mg size 0 capsules and 25 mg size 3 capsules. One batch of coated beads can be filled as a 75 mg strength batch or can be split to fill both 75 mg and 25 mg strengths, for example.

[0103] The 75 mg hard gelatin capsules were filled using an automated encapsulator at a speed of 80 - 100 spm to the target fill weight calculated to achieve 75 mg cysteamine free base per capsule. The 25 mg hard gelatin capsules were also filled with an automated encapsulator at a speed of 50-70 spm. The beads were introduced into the encapsulation process with a hopper.

Example 2 – Particle Size Distribution

[0104] Several lots of cysteamine bitartrate enteric-coated beads produced via an extrusion and spheronization process as described herein were analyzed for particle size distribution via analytical sieving. The results are tabulated below.

	% Retained	% Retained	% Retained	% Retained
Sieve Size (µm)	Lot A	Lot B	Lot C	Lot D
1700	0	0	0	0
1400	1.4	3.2	3.2	1.2
1180	19.5	25.7	26.7	20.3
1000	61.9	55.5	56	62
850	16.1	14.2	13.5	15.1
<850	1.2	1.4	0.6	1.4

Example 3 – Pharmacokinetics

[0105] A population PK study was performed using Cystagon[®] and capsules of cysteamine bitartrate gastro-resistant beads (CBGB) produced according to the method of Example 1 herein.

[0106] Pharmacokinetic (PK) and pharmacodynamic (PD) relationships following a single dose of CBGB capsules was first studied in comparison to a single dose of immediate-release cysteamine bitartrate in a study with 9 patients. Following normalization to a 450 mg dose, the maximum plasma levels C_{max}, AUC 0-6h and AUC 0-12h (calculated directly from the plasma level data for CBGB and from doubling the AUC 0-6h value for immediate-release cysteamine to represent two doses) were lower for CBGB (27.70 ± 14.99 µmol/L, 75.93 ± 39.22 µmol*h/L and 99.26 ± 44.21 µmol*h/L respectively) than for immediate-release cysteamine bitartrate (37.72 ± 12.10 µmol/L, 96.00 ± 37.81 µmol*h/L and 192.00 ± 75.62 µmol*h/L respectively). The pharmacokinetics of CBGB are consistent with a delayed-release formulation showing a T_{max} of 2.78 ± 1.56 h for CBGB cysteamine was moderately bound to human plasma proteins, predominantly to albumin, with mean protein binding of about 52%. Plasma protein binding was independent of concentration over the concentration range achieved clinically with the recommended doses.

[0107] Additional studies were carried out as follows.

[0108] CBGB-A Study

[0109] Cystagon[®] Treatment Assignment: one (1) pre-dose PD sample was collected at time 0 (i.e., within 15 minutes prior to the morning Cystagon[®] dose administration), considered as the time of trough cysteamine / peak of WBC cystine after administration of

immediate-release cysteamine bitartrate (Cystagon®). One (1) additional PD sample was collected at a sample timepoint that was time-matched to 1 of 3 PK sample profile times (either 2, 4 or 6 hours) post morning Cystagon® dose. There were six associated plasma PK samples collected at time 0 (within 15 minutes prior to morning Cystagon® dose); 30 minutes post morning Cystagon® dose; and 1, 2, 4 and 6 hours (immediately prior to the afternoon Cystagon® dose)

[0110] Inventive capsule Treatment Assignment: one (1) post-dose PD sample was collected at time 0.5 hour (30 minutes), considered as the time of trough cysteamine / peak of WBC cystine after administration of capsules of CBGB. Two (2) additional PD samples were collected at sample timepoints that were time-matched to PK sample profile times (either 3, 4, 8, 10 or 12 hours) post morning CBGB dose. In order to limit the impact of autocorrelation, juxtaposed times of sampling for patients treated with CBGB were not to be taken into account for the randomization. Therefore, patients were randomized to one of the following six pairs of the sampling time points: 3 and 8 hours, 3 and 10 hours, 3 and 12 hours, 4 and 8 hours, 4 and 10 hours, 4 and 12 hours. There were nine associated plasma PK samples collected at time 0 (within 15 minutes prior to morning CBGB dose), 30 minutes, 2, 3, 4, 6, 8, 10 and 12 hours post morning CBGB dose (immediately prior to the evening CBGB dose).

[0111] As recommended in the Cystagon® SmPC, food (meal or snack) was available 30 minutes prior to receiving the morning dose and (if applicable) the next Q6H of Cystagon® administration and the morning dose and Q12H CBGB administration and (if applicable) the next Q12H CBGB dose. Cystagon® was administered with water and CBGB was administered with an acidic beverage. Dairy products should have been withheld 1 hour before and after CBGB dosing.

[0112] CBGB-B Study

[0113] Administering cysteamine in fasted healthy volunteers provides very stable PK parameters such that it was possible to demonstrate bioequivalence between administrations of CBGB capsules as a whole or as their content sprinkled on food with only 20 healthy volunteers.

[0114] The PK parameters of cysteamine were determined after a single dose, first in fasted healthy volunteers, then in patients at steady state, using the model parameters obtained with healthy volunteers as starting parameters for the models in patients. Pharmacokinetic modeling of cysteamine was based on a 2-compartment model and

pharmacodynamic modeling of WBC cystine was based on an inhibitory E_{\max} model. (Belldina, E. B., M. Y. Huang, et al. (2003). "Steady-state pharmacokinetics and pharmacodynamics of cysteamine bitartrate in paediatric nephropathic cystinosis patients." Br J Clin Pharmacol 56(5): 520-525.)

[0115] Since CBGB studies in healthy volunteers were not done against Cystagon[®], data in fasted healthy volunteers (Gangoiti, J. A., M. Fidler, et al. (2010). "Pharmacokinetics of enteric-coated cysteamine bitartrate in healthy adults: a pilot study." Br J Clin Pharmacol 70(3): 376-382) were used to determine initial PK model parameters for Cystagon[®]. And data on EC-cysteamine (i.e. Eudragit L50D 55 enteric-coated capsules of Cystagon[®] - a different way of providing delayed-release cysteamine bitartrate) in this dataset was used for comparison purposes.

[0116] A bioequivalence designed to demonstrate bioequivalence between oral administration of intact CBGB capsules, and contents of opened CBGB capsules mixed with applesauce and taken orally. Twenty (20) healthy adults (mean age 37 years, range 19-64 years) received both presentations, 8 (75 mg) intact vs. 8 (75 mg) open capsules, in a crossover design study.

[0117] The final results are presented in the table below.

Study/ Protocol Country	Study Design	No. Subjects Entered/ Completed (M/F)	HV/P ^{a)} (Age: Mean, Range)	Treatment	Dose (mg)	Non-Compartmental Analysis (Pharsight, WinNonLin 6.2)				Population PK, 2-compartment Model (Pharsight, NLME 1.1)					
						T _{max} (min)	C _{max} (mg/L)	C _{max} _D (mg/L/mg)	AUC _{inf_D} (min*mg/L/mg)	T _{lag} (min)	Ka (1/min)	V/F (L)	Cl/F (L/min)	V ₂ (L)	Cl ₂ (L/min)
UCSD (USA)	Open label, Sequential	(4M/3F)/ (4M/3F)	P (12, 8-17)	Cystagon [®]	450	75 ± 19	3.1 ± 1.2	0.007 ± 0.003	0.88 ± 0.30	26	0.029	73	1.07	131	0.41
				EC- Cysteamine	450	220 ± 74	3.2 ± 1.4	0.007 ± 0.003	0.96 ± 0.40	156	0.025	98	1.17	54	0.5
CBGB-A (USA/ EU)	Random, Crossover	(24M/19F)/ (22M/16F)	P(12,6-26)	Cystagon [®]	250-750	74 ± 32	2.6 ± 1.4	0.006 ± 0.003	0.84 ± 0.31	23	0.025	94	1.1	191	0.5
				CBGB caps	425- 1300	183 ± 90	3.5 ± 1.7	0.005 ± 0.002	1.08 ± 0.46	60	0.015	87	1.2	200	0.4
CBGB-B (USA)	Random, Crossover	(13M/7F)/ (13M/7F)	HV(37, 19- 64)	CBGB caps	600	194 ± 38	2.3 ± 0.6	0.004 ± 0.001	0.84 ± 0.19	95	0.016	137	1.4	187	0.44
				CBGB sprinkled	600	190 ± 61	2.3 ± 0.7	0.004 ± 0.001	0.85 ± 0.21	98	0.017	151	1.4	192	0.47

^{a)} HV = Healthy Volunteers, P = Patients

[0118] The conclusion of this population PK modeling on two different presentations of CBGB (open and intact), is that the only difference between administering CBGB as intact capsules and as open capsules, sprinkled on applesauce, is expressed by the difference between lag times: as expected the start of absorption from the beads is still delayed (85 min) but slightly less than when the gelatin capsule has to be dissolved first (108 min) and this has not much of an impact on T_{max} (190 min for open capsules vs. 194 min for intact capsules) since probably only a small amount of beads dissolves early.

[0119] However, comparison between the two presentations of CBGB (open and intact) and the immediate-release cysteamine bitartrate (Cystagon[®]) and the delayed-release EC-cysteamine, shows that the absorption of cysteamine after CBGB dosing is not only more delayed (Cystagon[®] $T_{lag} \ll$ CBGB $T_{lag} \ll$ EC-cysteamine T_{lag}) but also further extended due to a slower absorption (CBGB $K_a \ll$ Cystagon[®] $K_a \approx$ EC-cysteamine K_a) compared to EC-cysteamine. Without intending to be bound by any particular theory, it is contemplated that the difference in absorption of the CBGB formulation is related to one or more factors including the distribution of bead sizes and time-progressive dissolution of multiple beads and/or the irregularity of bead shapes in the CBGB formulation and/or the distribution of enteric membrane thicknesses in the CBGB formulation.

Example 4 – Purity and Stability

[0120] Long term stability tests have been performed on the CBGB formulation made according to Example 1. The major impurity in the CBGB product is cystamine, the well known related substance (dimer).

[0121] The use of a more sensitive and less selective method has resulted in the observation of several impurities found in the CBGB formulation and the commercial product using cysteamine bitartrate, Cystagon[®]. Through the use of reverse phase HPLC, six peaks observed in the CBGB formulation related substances chromatograms have been identified as product degradants (specifically cysteamine bitartrate degradants). Two lots of Cystagon[®] were evaluated by the same test method. The impurities observed in representative CBGB chromatograms are also observed in Cystagon[®].

[0122] Impurities Assay Method

[0123] Cysteamine bitartrate samples are assessed by gradient elution HPLC using an XBRIDGE C18 column (dimensions: 150 mm × 4.6 mm; packing particle size: 3.5 μm) (Waters, Milford, Massachusetts). The autosampler temperature is 4°C. Approximately 10 μL or approximately 100 μL of sample is injected onto the column. The column temperature

is 40°C and the sample is eluted at a flow rate of 1.0 mL/min according to the following profile:

Time (min)	HPLC Gradient	
	Mobile Phase A (%)	Mobile Phase B (%)
0.0	100	0
2.0	100	0
20.0	60	40
25.0	60	40
25.1	100	0
40.0	100	0

[0124] Mobile Phase A contains 23.6 mM 1-octanesulfonic acid sodium and 29.0 mM sodium phosphate (pH 2.6)/acetonitrile/methanol 85/3/12 (v/v/v). Mobile Phase B contains 0.20 M 1-octanesulfonic acid sodium and 0.10 M sodium phosphate (pH 2.6)/acetonitrile/methanol 10/18/72 (v/v/v). The purity of 1-octanesulfonic acid is $\geq 98\%$. Detection is carried out using a UV detector at 210 nm.

[0125] **Reference Solution Preparation.** Reference solutions of Cysteamine Bitartrate Analytical Reference Standard are prepared as follows. Working Standard and Working Check Standard solutions are prepared having a nominal concentration of 0.54 mg/mL Cysteamine Bitartrate Analytical Reference Standard in Mobile Phase A using low actinic glassware. A Working Sensitivity solution is prepared having a nominal concentration of 0.30 mg/mL Cysteamine Bitartrate Analytical Reference Standard in Mobile Phase A using low actinic glassware, which corresponds to the limit of quantification (LOQ) for cysteamine. The water content of the Cysteamine Bitartrate Analytical Reference Standard is determined no more than 7 days before use by Karl Fischer titration or thermal gravimetric analysis (TGA). The Reference Standard is stored refrigerated and blanketed under nitrogen.

[0126] **Bead Prep Assay Sample Preparation.** Cysteamine Bitartrate Gastro-resistant Beads (CBGB) are prepared for analysis according to the following procedure. About 3.7 g of CBGB beads are ground to a fine powder using a ball mill for approximately 1 minute at 27 Hz. The grind is transferred to an amber bottle for storage. Stock Bead Prep Assay sample solutions are prepared in duplicate by adding $370.4 \text{ mg} \pm 5 \text{ mg}$ of the grind to a 250 mL low actinic volumetric flask and diluting with Mobile Phase A. The mixture is stirred with a stir bar for at least 15 minutes. Approximately 15 mL of the resulting solution is filtered through a 0.45 μm nylon filter, with the first 5 mL being discarded. The cysteamine concentration of the resulting Stock Bead Prep Assay sample solution is approximately 0.300

mg/mL. Working Bead Prep sample solutions are prepared by placing 4.0 mL of Stock Bead Prep Assay sample solution in a 25 mL low actinic volumetric flask and diluting to volume with Mobile Phase A. The cysteamine concentration of the resulting Working Bead Prep sample solution is approximately 0.048 mg/mL.

[0127] Assay Sample Preparation. CBGB capsules are prepared for analysis according to the following procedure. To reduce exposure to light and oxygen, sample preparation (from the initial weighing of the full capsules to the loading of sample vials on the HPLC) is completed in one day. Ten capsules are weighed. The capsule contents are emptied and the empty shells are weighed to determine the average capsule fill weight. The capsule contents are ground to a fine powder using a ball mill for approximately 1 minute at 27 Hz. The grind is transferred to an amber bottle for storage. Stock sample solutions are prepared in duplicate by adding the appropriate amount of the grind for 1 capsule (as determined by the average capsule fill weight) to a 25 mL low actinic volumetric flask and diluting with Mobile Phase A. The mixture is stirred with a stir bar for at least 15 minutes. The resulting solution is centrifuged at about 3400 rpm for 5 minutes. Approximately 15 mL of the centrifuged solution is filtered through a 0.45 μ m nylon filter (Acrodisc, 25 mm diameter), with the first 5 mL being discarded, to obtain Stock sample solutions. Working sample solutions are prepared by placing 6.0 mL of Stock sample solution (for 25 mg capsules) or 2.0 mL of Stock sample solution (for 75 mg capsules) in a 10 mL low actinic volumetric flask and diluting to volume with Mobile Phase A.

[0128] Content Uniformity Sample Preparation. CBGB capsules are prepared for analysis according to the following procedure. To reduce exposure to light and oxygen, sample preparation (from the initial weighing of the full capsules to the loading of sample vials on the HPLC) is completed in one day. Ten capsules are weighed. The contents of each capsule are emptied into separate mortars and the empty shells are weighed to determine the individual capsule fill weight. About 1-2 mL of Mobile Phase A is added into the mortar. The beads are immediately ground to a paste. If needed, additional Mobile Phase A is added to the paste, up to 5 mL total. The paste is transferred to a 250 mL low actinic volumetric flask. The mortar and pestle are thoroughly rinsed with Mobile Phase A and the rinse solution is collected in to the same flask. The flask is filled about three-quarters full with Mobile Phase A and stirred for at least 15 minutes. The flask is filled to volume with Mobile Phase A. Approximately 20 mL of the resulting solution is filtered through a 0.45 μ m nylon filter (Acrodisc, 25 mm diameter), with the first 5 mL being discarded, to obtain Stock CU sample solutions. Working CU sample solutions are prepared by placing 12.0 mL of Stock

CU sample solution (for 25 mg capsules) or 4.0 mL of Stock CU sample solution (for 75 mg capsules) in a 25 mL low actinic volumetric flask and diluting to volume with Mobile Phase A. The cysteamine concentration of the resulting Working CU sample solutions is approximately 0.048 mg/mL.

[0129] Data Analysis. The cysteamine Working Standard solution concentration is calculated according to the following equation: Cysteamine Concentration (C_{std}) = mg Cysteamine Bitartrate Analytical Reference Standard $\times P_f$ / 25.0 mL

[0130] P_f represents a purity factor for the standard material. P_f is calculated according to the following equation: $P_f = B \times (100 - \text{Water}) \times C / 100$

where B = the anhydrous cysteamine free base in the Cysteamine Bitartrate Analytical Reference Standard (expressed as a decimal value on the standard bottle label),
water = the water content as determined by Karl Fischer or TGA no more than 7 days before use (expressed as a percentage), and
C = the cystamine correction (expressed as a decimal value on the standard bottle label).

[0131] The amount of cysteamine per capsule is calculated according to the following equation: mg cysteamine per capsule = $(A_{Sam}/A_{Std}) \times C_{Std} \times DF \times (AveWt/SamWt)$

where A_{Sam} = the peak area of cysteamine in the sample chromatogram with a 10 μ L injection,

A_{Std} = the average peak area of cysteamine in all Working Standard solution chromatograms with a 10 μ L injection,

C_{Std} = the concentration (mg/mL) of cysteamine in the Working Standard solution,

DF = the dilution factor (125 for 75 mg capsules; 41.6667 for 25 mg capsules),

AveWt = the average capsule fill weight (mg), and

SamWt = the sample weight (mg).

[0132] For Content Uniformity, the amount of cysteamine per capsule is calculated according to the following equation: mg cysteamine per capsule =

$$(A_{Sam}/A_{Std}) \times C_{Std} \times DF$$

where A_{Sam} = the peak area of cysteamine in the sample chromatogram with a 10 μ L injection,

A_{Std} = the average peak area of cysteamine in all Working Standard solution chromatograms with a 10 μ L injection,

C_{Std} = the concentration (mg/mL) of cysteamine in the Working Standard solution, and
 DF = the dilution factor (1562.5 for 75 mg capsules; 520.8 for 25 mg capsules).

[0133] For the Bead Prep Assay, the amount of cysteamine per capsule is calculated according to the following equation: mg cysteamine per capsule =

$$(A_{Sam}/A_{Std}) \times C_{Std} \times DF \times (AveWt/SamWt)$$

where A_{Sam} = the peak area of cysteamine in the sample chromatogram with a 10 μ L injection,

A_{Std} = the average peak area of cysteamine in all Working Standard solution chromatograms with a 10 μ L injection,

C_{Std} = the concentration (mg/mL) of cysteamine in the Working Standard solution,

DF = the dilution factor (use the 75 mg Dilution Factor, 1562.5),

$AveWt$ = the average capsule fill weight (mg) (use the target fill weight, 370.4 mg), and

$SamWt$ = the sample weight (mg) (use the actual weight used in sample preparation).

[0134] The percentage of the label claim (%LC) is calculated for the Assay, Content Uniformity, and Bead Prep Assay sample solutions according to the following equation:

$$\%LC = (mg \text{ cysteamine})/LC \times 100\%$$

where mg cysteamine = the amount calculated by the applicable equation above, and

LC = the amount of the label claim (75 mg or 25 mg) (use 75 mg for the Bead Prep Assay).

[0135] The amount of substances related to cysteamine bitartrate (including cysteamine impurities) such as cystamine is calculated according to the following equation:

$$mg \text{ related substance} = (A_{RS}/A_{Std}) \times (C_{Std}/RRF) \times DF \times (AveWt/SamWt)$$

where A_{RS} = the peak area of any related substance in the Working sample solution chromatogram with a 100 μ L injection (peaks before RRT 0.48 are disregarded; peaks observed in the chromatogram of the second injection of Mobile Phase A/Blank (100 μ L injection) are also disregarded),

A_{Std} = the average peak area of cysteamine in all Working Standard solution chromatograms with a 10 μ L injection,

C_{Std} = the concentration (mg/mL) of cysteamine in the Working Standard solution,

RRF = the relative response factor (0.98 for cystamine; 1.00 for other related substances),

DF = the dilution factor (12.5 for 75 mg capsules; 4.16667 for 25 mg capsules),

$AveWt$ = the average capsule fill weight (mg), and

$SamWt$ = the weight the sample grind from the Working sample solution preparation (mg).

[0136] The weight percentage of cystamine and other individual related substances is determined according to the following equation:

$$\% \text{ individual related substance} = \text{mg related substance} / \text{mg cysteamine} \times 100\%$$

where mg related substance = the amount of related substance calculated above, and
mg cysteamine = the amount of cysteamine for the Assay sample.

[0137] The percentage of total related substances is determined by summing all related substances greater than or equal to 0.05%. Peaks after 28 minutes are disregarded. In contrast to a previous electrochemical detection method that disregarded early-eluting peaks as not relevant to the purity calculation, the foregoing method determines that early peaks are impurities and integrates early-eluting peaks as described above.

[0138] Results

[0139] Two lots of Cystagon[®] were dispensed in standard pharmacy containers and verified to be well within the manufacturer's expiration date. One lot was provided by a healthcare provider. It was dispensed in a standard pharmacy bottle and verified by the healthcare provider to be well within the expiration date. Upon analysis by the Test Method, it was shown to contain 9.1% cystamine by weight and 10.3% total related substances, based on the weight of cysteamine, using the assay described above. The second analyzed Cystagon[®] lot was identified by lot number. Upon analysis by the assay described above, it was shown to contain 5.2% cystamine by weight and 5.7% total related substances, based on the weight of cysteamine. Each Cystagon[®] lot was shipped and stored under specified label conditions.

[0140] Two representative lots of the CBGB capsule formulation were analyzed by the assay described above and were shown to contain 3.7% cystamine by weight and 3.6% cystamine by weight, respectively, based on the weight of cysteamine, at the time of manufacture. For both lots, the total amount of related substances was 4.2% by weight, based on the weight of cysteamine.

[0141] The CBGB product lots were put on stability testing in various packages and storage conditions, then assayed for purity using the assay described above. The results are shown in the table below

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Lot	Product	Conditions	Cystamine % / total related substances at time point (month)						
			Initial	1	2	3	6	9	12
1	75 mg / 60 / 100 cc	25 / 60	3.7 / 4.2	3.7 / NA	3.1 / NA	3.4 / 4.2	3.5 / 4.4	3.7 / 5.1	3.8 / 5.5
1	75 mg / 60 / 100 cc	40 / 75	3.7 / 4.2	3.7 / NA	3.2 / NA	3.5 / 7.9	3.9 / 12.3		
1	75 mg / 150 / 250 cc	25 / 60	3.7 / 4.2	3.5 / NA	3.4 / NA	3.7 / 4.5	3.6 / 4.3	3.6 / 4.9	3.7 / 5.4
1	75 mg / 150 / 250 cc	40 / 75	3.7 / 4.2	3.4 / NA	3.4 / NA	3.7 / 7.9	3.8 / 11.6		
1	75 mg / 300 / 400 cc	25 / 60	3.7 / 4.2	3.5 / NA	3.3 / NA	3.4 / 4.2	3.5 / 4.4	3.7 / 5.1	3.8 / 5.7
1	75 mg / 300 / 400 cc	40 / 75	3.7 / 4.3	3.4 / NA	3.2 / NA	3.6 / 7.7	4.0 / 12.8		
1	75 mg / 60 / bulk	25 / 40	3.7 / 4.2	3.4 / NA	3.4 / NA	3.2 / NA	3.3 / 4.2	3.3 / 4.5	3.2 / 4.6
1	75 mg / 60 / bulk	40 / 75	3.7 / 4.2	3.4 / NA	3.2 / NA	3.3 / NA	2.9 / 9.1		
2	75 mg / 150 / 250 cc	25 / 60	3.6 / 4.2	3.1 / 4.0	3.3 / 4.3	3.0 / 4.3	3.3 / 5.0		
2	75 mg / 150 / 250 cc	40 / 75	3.6 / 4.2	3.1 / 7.5	3.6 / 12.1				

[0142] Additional CBGB product samples according to Example 1 were put on long term stability testing in various packages and storage conditions, then assayed for purity using the assay described above. Results are shown in the table below.

Lot	Product	Conditions	Cystamine % / total related substances at time point (month)									
			Initial	1	2	3	6	9	12	15	18	24
3	25 mg / 60 / 50 cc	25 / 60	3.2 / 4.1	3.0 / NA	3.3 / NA	3.1 / 4.2	3.3 / 4.7	3.2 / 4.9	3.6 / 5.5	NA	4.0 / 6.8	4.6 / NA
3	25 mg / 60 / 50 cc	40 / 75	3.2 / 4.1	2.9 / NA	3.0 / NA	3.0 / 7.8	3.7 / 13.4					
4	75 mg / 150 / 250 cc	25 / 60	3.2 / 4.0	3.2 / NA	3.4 / NA	3.4 / 4.7	3.7 / 5.2	3.5 / 5.3	4.1 / 6.3	NA	4.2 / 7.1	4.7 / NA
4	75 mg / 150 / 250 cc	40 / 75	3.2 / 4.0	3.1 / NA	3.4 / NA	3.5 / 9.0	4.0 / 13.8					

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Lot	Product	Conditions	Cystamine % / total related substances at time point (month)									
			Initial	1	2	3	6	9	12	15	18	24
5	75 mg / 60 / 100 cc	25 / 60	3.4 / 4.2	3.4 / NA	3.5 / NA	3.3 / 4.4	3.7 / 5.2	3.5 / 5.2	5.0 / NA	3.9 / 6.0	3.9 / NA	5.3 / NA
5	75 mg / 60 / 100 cc	40 / 75	3.4 / 4.2	3.3 / NA	3.4 / NA	3.3 / 8.5	4.1 / 16.0 ¹					
5	75 mg / 300 / 400 cc	25 / 60	3.4 / 4.2	3.5 / NA	3.5 / NA	3.5 / 4.9	4.0 / 6.0	3.3 / 5.3	5.3 / NA	4.1 / 6.5	4.1 / NA	5.3 / NA
5	75 mg / 300 / 400 cc	40 / 75	3.4 / 4.2	3.5 / NA	3.7 / NA	3.7 / 9.6	4.2 / 15.4 ¹					
5	75 mg / 60 / bulk	25 / 60	3.4 / 4.2	3.5 / NA	3.5 / NA	3.4 / NA	3.7 / 5.2	3.2 / NA	4.1 / 5.5			
5	75 mg / 60 / bulk	40 / 75	3.4 / 4.2	3.4 / NA	3.4 / NA	3.1 / NA	3.0 / 11.2					
6	25 mg / 60 / 50 cc	25 / 60	3.3 / 4.1	3.3 / NA	3.2 / NA	3.2 / 4.3	3.7 / 5.5	3.3 / 5.0	4.0 / NA	3.9 / 5.9	4.4 / NA	5.1 / NA
6	25 mg / 60 / 50 cc	40 / 75	3.3 / 4.1	3.2 / NA	3.1 / NA	3.0 / 7.8	3.8 / 15.7 ¹					
6	25 mg / 420 / 250 cc	25 / 60	3.3 / 4.1	3.3 / NA	3.5 / NA	3.6 / 4.9	4.0 / 6.0	3.8 / 5.9	4.6 / NA	4.8 / 7.4	4.1 / NA	5.2 / NA
6	25 mg / 420 / 250 cc	40 / 75	3.3 / 4.1	3.4 / NA	3.5 / NA	3.5 / 9.7	4.7 / 17.1 ¹					
6	25 mg / 60 / bulk	25 / 60	3.3 / 4.1	3.4 / NA	3.4 / NA	3.3 / NA	3.7 / 5.4	3.1 / NA	3.5 / 5.3			
6	25 mg / 60 / bulk	40 / 75	3.3 / 4.1	3.3 / NA	3.2 / NA	2.9 / NA	2.9 / 11.4					
7	75 mg / 60 / 100 cc	25 / 60	3.2 / 3.9	3.2 / NA	3.3 / NA	3.3 / 4.5	3.5 / 5.3	3.2 / 4.9	4.6 / NA	4.1 / 6.1	3.6 / NA	4.6 / NA
7	75 mg / 60 / 100 cc	40 / 75	3.2 / 3.9	3.2 / NA	3.1 / NA	3.2 / 8.0	3.7 / 13.5 ¹					
7	75 mg / 300 / 400 cc	25 / 60	3.2 / 3.9	3.4 / NA	3.4 / NA	3.4 / 4.8	3.7 / 5.5	3.4 / 5.2	4.9 / NA	4.2 / 6.4	3.8 / NA	4.7 / NA

¹ Samples pulled at 6 months but held at room temperature until new reference standard was qualified (at 8 months)

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Lot	Product	Conditions	Cystamine % / total related substances at time point (month)									
			Initial	1	2	3	6	9	12	15	18	24
	dose/count/bottle size	°C / % RH										
7	75 mg / 300 / 400 cc	40 / 75	3.2 / 3.9	3.3 / NA	3.3 / NA	3.5 / 9.1	3.9 / 13.6 ¹					
7	75 mg / 60 / bulk	25 / 60	3.2 / 3.9	3.3 / NA	3.3 / NA	3.2 / NA	3.5 / 5.2	2.9 / NA	4.0 / 5.5			
7	75 mg / 60 / bulk	40 / 75	3.2 / 3.9	3.2 / NA	3.2 / NA	2.9 / NA	2.8 / 10.3					
8	25 mg / 60 / 50 cc	25 / 60	3.1 / 3.9	3.1 / NA	3.1 / NA	3.0 / 4.1	3.4 / 4.9	3.1 / 4.9	3.7 / NA	3.4 / 5.3	3.4 / NA	4.3 / NA
8	25 mg / 60 / 50 cc	40 / 75	3.1 / 3.9	3.0 / NA	2.9 / NA	2.7 / 7.4	3.4 / 13.4 ¹					
8	25 mg / 420 / 250 cc	25 / 60	3.1 / 3.9	3.2 / NA	3.3 / NA	3.3 / 4.6	3.6 / 5.3	3.4 / 5.0	4.1 / NA	4.5 / 6.8	3.8 / NA	4.6 / NA
8	25 mg / 420 / 250 cc	40 / 75	3.1 / 3.9	3.3 / NA	3.3 / NA	3.2 / 9.1	4.0 / 16.2 ¹					
8	25 mg / 60 / bulk	25 / 60	3.1 / 3.9	3.3 / NA	3.2 / NA	3.1 / NA	3.3 / 4.7	3.0 / NA	3.4 / 4.9			
8	25 mg / 60 / bulk	40 / 75	3.1 / 3.9	3.2 / NA	3.0 / NA	2.8 / NA	2.7 / 10.6					
9	25 mg / 60 / 50 cc	25 / 60	3.6 / 4.2	3.5 / NA	2.9 / NA	3.2 / 4.0	3.4 / 4.4	3.3 / 4.6	3.4 / 5.0			
9	25 mg / 60 / 50 cc	40 / 75	3.6 / 4.2	3.4 / NA	2.7 / NA	3.0 / 6.8	3.4 / 11.4					
9	25 mg / 420 / 250 cc	25 / 60	3.6 / 4.2	3.5 / NA	3.0 / NA	3.4 / 4.3	3.4 / 4.4	3.5 / 5.0	3.8 / 5.8			
9	25 mg / 420 / 250 cc	40 / 75	3.6 / 4.2	3.5 / NA	3.0 / NA	3.5 / 7.9	3.8 / 12.9					
9	25 mg / 60 / bulk	25 / 40	3.6 / 4.2	3.5 / NA	3.0 / NA	3.3 / NA	3.3 / 4.2	3.1 / 4.2	3.1 / 4.6			
9	25 mg / 60 / bulk	40 / 75	3.6 / 4.2	3.3 / NA	2.8 / NA	3.0 / NA	2.8 / 9.1					
10	25 mg / 60 / 50 cc	25 / 60	3.4 / 4.0	NA	NA	3.1 / 3.9	3.1 / 4.1	2.9 / 4.2	3.1 / 4.7			

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Lot	Product	Conditions	Cystamine % / total related substances at time point (month)									
			Initial	1	2	3	6	9	12	15	18	24
10	dose/count/bottle size 25 mg / 60 / 50 cc	40 / 75	3.4 / 4.0	NA	NA	2.7 / 7.0	3.2 / 11.9					

¹ Samples pulled at 6 months but held at room temperature until new reference standard was qualified (at 8 months)

[0143] All of the foregoing CBGB samples met the acid resistance criteria (Not more than 10% (Q) of the label claim of cysteamine is dissolved after 2 hours in 0.1N HCl) and dissolution criteria (Not less than 70% (Q) of the label claim of cysteamine is dissolved after 30 minutes in 0.2M sodium phosphate buffer, pH 6.8)

[0144] The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art.

[0145] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise" and variations such as "comprises" and "comprising" will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0146] Throughout the specification, where compositions are described as including components or materials, it is contemplated that the compositions can also consist essentially of, or consist of, any combination of the recited components or materials, unless described otherwise. Likewise, where methods are described as including particular steps, it is contemplated that the methods can also consist essentially of, or consist of, any combination of the recited steps, unless described otherwise. The invention illustratively disclosed herein suitably may be practiced in the absence of any element or step which is not specifically disclosed herein.

[0147] The practice of a method disclosed herein, and individual steps thereof, can be performed manually and/or with the aid of or automation provided by electronic equipment. Although processes have been described with reference to particular embodiments, a person of ordinary skill in the art will readily appreciate that other ways of performing the acts associated with the methods may be used. For example, the order of various of the steps may

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be changed, unless described otherwise. In addition, some of the individual steps can be combined, omitted, or further subdivided into additional steps.

CLAIMS:

1. A pharmaceutical dosage form comprising delayed-release cysteamine beads, the beads comprising:
 - (i) a core particle comprising a mixture of cysteamine bitartrate and a binder, and
 - (ii) an enteric membrane surrounding the core particle;
 wherein the beads have a distribution of particle sizes in a range of about 0.7 mm to about 2.8 mm;
 wherein the enteric membrane begins to dissolve within a pH range of about 4.5 to about 6.5;
 wherein the enteric membrane is present in an amount in a range of about 20% to about 40% by weight, based on the weight of the core particles; and
 wherein the pharmaceutical dosage form, upon administration to cystinosis patients at 425 mg to 1300 mg free cysteamine base during treatment, provides:
 - (a) a mean C_{max} upon oral dosing, in a range of about 3.5 ± 1.7 mg/L or in a range of 80% to 125% thereof; and
 - (b) a mean AUC (0-inf_D) upon oral dosing, in a range of about 1.08 ± 0.46 min*mg/L/mg or in a range of 80% to 125% thereof.
2. The pharmaceutical dosage form of claim 1, wherein the cysteamine as free base comprises at least 10 wt.% of the core particle.
3. The pharmaceutical dosage form of claim 1, wherein the enteric membrane is present in an amount in a range of about 25% to about 35% by weight, based on the weight of the core particles.
4. The pharmaceutical dosage form of claim 1, wherein the cysteamine bitartrate comprises at least 50 wt.% of the core particle.
5. The pharmaceutical dosage form of claim 1, wherein the beads provide a mean C_{max} and mean AUC (0-inf_D) upon oral dosing, fasted, when administered inside a capsule shell that are bioequivalent to the mean C_{max} and mean AUC (0-inf_D) upon oral dosing, fasted, when administered without a capsule shell.

6. The pharmaceutical dosage form of claim 1, wherein the enteric membrane comprises an enteric material that begins to dissolve at pH of about 5.5 in an aqueous solution.
7. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical dosage form, upon administration to cystinosis patients at 425 mg to 1300 mg free cysteamine base during treatment, provides:
 - (a) a mean Cmax upon oral dosing, in a range of about 3.5 ± 1.7 mg/L; and
 - (b) a mean AUC (0-inf_D) upon oral dosing, in a range of about 1.08 ± 0.46 min*mg/L/mg.
8. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical dosage form, upon administration to cystinosis patients at 425 mg to 1300 mg free cysteamine base during treatment, provides:
 - (a) a mean Cmax upon oral dosing, of 3.5 mg/L or in a range of 80% to 125% thereof; and
 - (b) a mean AUC (0-inf_D) upon oral dosing, of 1.08 min*mg/L/mg or in a range of 80% to 125% thereof.
9. A pharmaceutical dosage form, comprising delayed-release cysteamine beads, the beads comprising:
 - (i) a core particle comprising cysteamine or a pharmaceutically acceptable salt thereof and a binder, and
 - (ii) an enteric membrane surrounding the core particle,
 wherein the beads have a distribution of particle sizes in a range of about 0.7 mm to about 2.8 mm;
 wherein the enteric membrane begins to dissolve within a pH range of about 4.5 to about 6.5;
 wherein the enteric membrane is present in an amount in a range of about 20% to about 40% by weight, based on the weight of the core particles; and
 wherein the pharmaceutical dosage form, upon administration in a capsule to fasted healthy normal subjects at 600 mg free cysteamine base, provides:
 - (a) a mean Cmax upon oral dosing in a range of 2.3 ± 0.6 mg/L or in a range of 80% to 125% thereof; and

(b) a mean AUC (0-inf_D) upon oral dosing in a range of $0.84. \pm 0.19$ min*mg/L/mg or in a range of 80% to 125% thereof.

10. The pharmaceutical dosage form of claim 9, wherein the enteric membrane is present in an amount in a range of about 25% to about 35% by weight, based on the weight of the core particles.
11. The pharmaceutical dosage form of claim 9, wherein the particle sizes of the beads are in a range of about 0.7 mm to about 2.5 mm.
12. The pharmaceutical dosage form of claim 9, wherein the distribution of bead sizes is characterized by at least 80% by weight of the beads having a particle size in a range of about 850 μ m to about 1180 μ m.
13. The pharmaceutical composition of claim 9, wherein 5% or less of the beads by weight are retained on a #12 mesh (1.68 mm) screen and 10% or less by weight pass through a #20 mesh (0.84 mm) screen.
14. The pharmaceutical composition of claim 9, wherein the distribution of bead sizes is characterized by less than 5% by weight of the beads being retained on a 1400 μ m sieve.
15. The pharmaceutical dosage form of claim 9, wherein the distribution of bead sizes is characterized by less than 30% by weight of the beads being retained on a 1180 μ m sieve.
16. The pharmaceutical dosage form of claim 9, wherein the distribution of bead sizes is characterized by less than 70% by weight of the beads being retained on a 1000 μ m sieve.
17. The pharmaceutical dosage form of claim 9, wherein the distribution of bead sizes is characterized by less than 20% by weight of the beads being retained on a 850 μ m sieve.
18. The pharmaceutical dosage form of claim 9, wherein the distribution of bead sizes is characterized by at least 15% by weight of the beads being retained on a 1180 μ m sieve.

19. The pharmaceutical dosage form of claim 9, wherein the distribution of bead sizes is characterized by at least 50% by weight of the beads being retained on a 1000 μm sieve.
20. The pharmaceutical dosage form of claim 9, wherein the distribution of bead sizes is characterized by at least 10% by weight of the beads being retained on a 850 μm sieve.
21. The pharmaceutical dosage form of claim 9, wherein the distribution of bead sizes is characterized by a median particle size in a range of about 850 μm to about 1180 μm .
22. The pharmaceutical dosage form of claim 9, wherein the bead core particle further comprises a filler.
23. The pharmaceutical dosage form of claim 9, wherein the cysteamine as free base is present in the bead core particle in an amount of at least 10 wt. %.
24. The pharmaceutical dosage form of claim 9, wherein the cysteamine or pharmaceutically acceptable salt thereof is a pharmaceutically acceptable salt of cysteamine.
25. The pharmaceutical dosage form of claim 9, wherein 5% or less of the bead core particles by weight are retained on a #12 mesh (1.68 mm) screen and 10% or less by weight pass through a #20 mesh (0.84 mm) screen.
26. The pharmaceutical dosage form of claim 9, wherein the enteric-coated beads are characterized by acid resistance such that not more than 10% of the cysteamine in the beads is dissolved after a period of two hours in a 0.1N HCl solution.
27. The pharmaceutical dosage form of claim 9, wherein the enteric-coated beads are characterized by dissolution such that 80% of the cysteamine or pharmaceutically acceptable salt thereof is released within 20 minutes in a solution buffered at pH 6.8.

28. The pharmaceutical dosage form of claim 9, further comprising a capsule shell enclosing the plurality of beads.

29. The pharmaceutical dosage form of claim 9, wherein the beads provide a mean C_{max} and mean AUC (0-inf_D) upon oral dosing, fasted, when administered inside a capsule shell that are bioequivalent to the mean C_{max} and mean AUC (0-inf_D) upon oral dosing, fasted, when administered without a capsule shell.

30. The pharmaceutical dosage form of claim 9, wherein the enteric membrane comprises an enteric material that begins to dissolve at pH of about 5.5 in an aqueous solution.

31. The pharmaceutical dosage form of claim 9, wherein the pharmaceutical dosage form, upon administration in a capsule to fasted healthy normal subjects at 600 mg free cysteamine base, provides:

- (a) a mean C_{max} upon oral dosing in a range of 2.3. \pm 0.6 mg/L; and
- (b) a mean AUC (0-inf_D) upon oral dosing in a range of 0.84. \pm 0.19 min*mg/L/mg.

32. The pharmaceutical dosage form of claim 9, wherein the pharmaceutical dosage form, upon administration in a capsule to fasted healthy normal subjects at 600 mg free cysteamine base, provides:

- (a) a mean C_{max} upon oral dosing of 2.3 mg/L or in a range of 80% to 125% thereof; and
- (b) a mean AUC (0-inf_D) upon oral dosing of 0.84 min*mg/L/mg or in a range of 80% to 125% thereof.