

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kathlene Powell et al.

Application No.: 14/751,639

Confirmation No.: 9246

Filed: June 26, 2015

Art Unit: 1613

For: Delayed Release Cysteamine Bead Formulation,
and Methods of Making and Using Same

Examiner: Phan, Doan

DECLARATION UNDER 37 C.F.R. 1.132

I, Christopher Rubino, Pharm.D., hereby declare as follows:

1. I am currently the Executive Vice President, Pharmacometrics, at the Institute for Clinical Pharmacodynamics. In my position I focus on the utilization of pharmacokinetic and pharmacodynamic (PK-PD) principles in the areas of drug development. I also have expertise in pediatric pharmacology. My experience in this area spans the full breadth of activities from designing studies in adults and children to analysis of PK-PD data from such studies and, ultimately, to presentation at regulatory and international scientific meetings. I have served as a resource for pharmaceutical firms during the submission of adult- and pediatric-related filings to the FDA in several therapeutic areas, and I have evaluated PK-PD data for a number of different types of drug formulations including drugs comprising enteric coatings. Additionally, I am the author or coauthor of over 30 peer-reviewed scientific publications and approximately 75 scientific abstracts. My curriculum vitae is attached.
2. I am qualified by my education and experience to explain what one of ordinary skill in the art would have understood as of June 17, 2013.
3. I make this declaration in my personal capacity and not on behalf of Raptor Pharmaceutical Corp. I have been retained by Raptor as an expert in the relevant field to provide my opinions regarding pharmacokinetics, as described below. I am being

compensated for my time at my normal, hourly consulting rate. My compensation is not dependent on, and in no way affects, the substance of my statements in this declaration.

4. I have reviewed U.S. patent publication no. 2009/0076166, particularly the pharmacokinetic data in Figure 6.
5. I have reviewed the examples of the above-identified application, particularly the pharmacokinetic data in the table at paragraph [00117] at page 26.
6. I have also been informed that the pending claims of the above-identified application have been amended as they appear in Exhibit A.
7. The patent application indicates that the pharmacokinetic data in the 5th data row of the table at page 26 has been generated from delayed-release cysteamine beads that fall within the claims in Exhibit A. In particular, the beads (a) comprise an enteric membrane that begins to dissolve within a pH range of about 4.5 to about 6.5, in an amount within the range of about 20% to about 40% by weight, and (b) have a distribution of sizes in a range of about 0.7 mm to about 2.8 mm. The pharmacokinetic data in the table at page 26 shows that when orally administered in a capsule to fasted healthy normal subjects at single dose of 600 mg free cysteamine base, the beads provide a pharmacokinetic profile that includes a mean C_{max} of 2.3 ± 0.6 mg/L and a mean AUC (0-inf_D) of 0.84 ± 0.19 min*mg/L/mg, among other pharmacokinetic parameters.
8. I have used this pharmacokinetic data referenced in paragraph 6 above to create a graph representing the two-compartment PK model curve, graphed as µg/ml plasma cysteamine concentration over time, shown as the thick line in Exhibit B.
9. Figure 6 of U.S. patent publication no. 2009/0076166 shows plasma cysteamine concentration over time after oral administration to a cystinosis patient of a single dose of 450 mg free cysteamine base, in the form of capsules enterically coated with Eudragit L30 D-55. (I understand that the particular coating material is specified in the related publication by Gangoiiti et al., "Pharmacokinetics of Enteric-Coated Cysteamine Bitartrate in Healthy Adults: A Pilot Study," Br. J. Clin. Pharmacol., 70(3):376-382 (published online June 8, 2010).) I have graphed the data shown in Figure 6 as the thin line in Exhibit B.
10. As illustrated in Exhibit B, the pharmacokinetic profile of the capsule dosage form represented in Figure 6 of U.S. patent publication no. 2009/0076166 is unexpectedly markedly different from the pharmacokinetic profile of the beads of the present invention,

shown in the 5th data row of the table at page 26 of the above-identified application, despite that both dosage forms contained cysteamine as the active ingredient, and contained the same Eudragit L30 D-55 enteric coating material.

11. Upon reviewing U.S. patent publication no. 2009/0076166, one of ordinary skill in the art could not have predicted that formulating cysteamine as delayed-release cysteamine beads that (a) comprise an enteric membrane that begins to dissolve within a pH range of about 4.5 to about 6.5, in an amount within the range of about 20% to about 40% by weight, and (b) have a distribution of sizes in a range of about 0.7 mm to about 2.8 mm, would have resulted in the pharmacokinetic profile of the beads shown in the 4th, 5th and 6th rows of data in the table at page 26 of the above-identified application. Thus, the pharmacokinetic profile of the beads was unexpected.

Certification

12. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. § 1001), and may jeopardize the validity of the application or any patent issuing thereon.

25 Aug 2015

DATE



Christopher Rubino, Pharm.D.

EXHIBIT A

1. (new) 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. (new) The pharmaceutical dosage form of claim 21, wherein the cysteamine (as free base) comprises at least 10 wt.% of the core particle.

3. (new) The pharmaceutical dosage form of claim 21, 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. (new) The pharmaceutical dosage form of claim 21, wherein the cysteamine or pharmaceutically acceptable salt thereof is cysteamine bitartrate.

5. (new) The pharmaceutical dosage form of claim 24, wherein the cysteamine bitartrate comprises at least 50 wt.% of the core particle.

6. (new) The pharmaceutical dosage form of claim 21, 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.

7. (new) The pharmaceutical dosage form of claim 21, wherein the enteric membrane comprises an enteric material that begins to dissolve at pH of about 5.5 in an aqueous solution.

8. (new) The pharmaceutical dosage form of claim 21, 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; and
- (b) a mean AUC (0-inf_D) upon oral dosing, in a range of about 1.08 ± 0.46 min*mg/L/mg.

9. (new) The pharmaceutical dosage form of claim 21, 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, 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.

10. (new) 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 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 ± 0.19 min*mg/L/mg or in a range of 80% to 125% thereof.

11. (new) The pharmaceutical dosage form of claim 30, wherein the cysteamine (as free base) comprises at least 10 wt.% of the core particle.

12. (new) The pharmaceutical dosage form of claim 30, 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.

13. (new) The pharmaceutical dosage form of claim 30, wherein the cysteamine or pharmaceutically acceptable salt thereof is cysteamine bitartrate.

14. (new) The pharmaceutical dosage form of claim 33, wherein the cysteamine bitartrate comprises at least 50 wt.% of the core particle.

15. (new) The pharmaceutical dosage form of claim 30, wherein the beads provide a mean Cmax and mean AUC (0-inf_D) upon oral dosing, fasted, when administered inside a capsule shell that are bioequivalent to the mean Cmax and mean AUC (0-inf_D) upon oral dosing, fasted, when administered without a capsule shell.

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

17. (new) The pharmaceutical dosage form of claim 30, 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; and

(b) a mean AUC (0-inf_D) upon oral dosing in a range of 0.84 ± 0.19 min*mg/L/mg.

18. (new) The pharmaceutical dosage form of claim 30, 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.

EXHIBIT B