# ADDENDUM TO CLINICAL PHARMACOLOGY REVIEW

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| Submission | **NDA 203-389/S-10** |
| Submission Date | **July 14, 2014** |
| Generic Name | **Cysteamine Bitartrate (Procysbi® Delayed-Release Capsule)** |
| Clinical Pharmacology Reviewer | **Insook Kim, Ph.D.** |
| Clinical Pharmacology TL | **Sue-Chih Lee, Ph.D.** |
| Pharmacometrics TL | **Justin Earp, Ph.D.** |
| DCP3 Division Director | **Capt. E. Dennis Bashaw, Pharm.D.** |
| OCP Division | **DCP3/ DPM** |
| OND division | **DGIEP** |
| Applicant | **Raptor** |
| Formulation; Strength(s) | **25-mg and 75-mg Capsule** |
| Proposed Indication | **Management of nephropathic cystinosis children ages 2 to 5 years** |
| Approved/Proposed Dosing Regimen | **1.3 g/m$^2$/day in two divided doses, every 12 hours, for patients who are switching from Cystagon®,** (b) (4) |

## 1. EXECUTIVE SUMMARY

This is an addendum to the Clinical Pharmacology Review of NDA 203-389 Supplement 10 to discuss a Post-Marketing Study. The NDA 203-389 Supplement 10 was submitted in support of expansion of the approved indication to younger patients 2-5 years old, inclusive. This addendum is also to summarize the sponsor's amendment dated 6/30/15. The review of clinical pharmacology found the Supplement 10 acceptable from a clinical pharmacology standpoint. The review of sponsor's amendment dated 6/30/15 does not change the clinical pharmacology review conclusion. See the clinical pharmacology review of NDA 203-389 dated 6/29/15 for more details.

## 1.1. Recommendations

## 1.2. Post-Marketing Commitments

*Study: In vivo* study to evaluate the effects of administration methods on pharmacokinetics of cysteamine. In this study the pharmacokinetics of cysteamine will be compared between after administration of Procysbi® capsules with water and with orange juice. Also the effects of a concomitant proton-pump inhibitor on the pharmacokinetics of cysteamine after administration of Procysbi® with water will be studied.

*Rationale*

Procysbi is a hard gelatin capsule containing enteric-coated (b) (4) In clinical trials, Procysbi was administered with acidic beverage such as orange juice by most patients with a few exceptions per protocol to avoid premature release of cysteamine. It was noted that in clinical trial, 58% of patients used concomitant gastric acid reducers such as proton pump inhibitors or $H_2$-receptor antagonists while 42% of patients did not use gastric acid reducers.

A flexibility of administration method i.e. administration with water, is of importance for compliance and in avoidance of unnecessary consumption of acidic beverage for a life-long treatment especially for pediatric patients[1]. However there is no adequate information on whether administration of Procysbi capsules with acidic beverage by all patients is necessary especially when patients are not on concomitant gastric acid reducers as well as when patients are on concomitant gastric acid reducers.

This post-marketing study will clarify the potential effects of administration methods for Procysbi and the results will be used to better inform the labeling.

## 1.3. Summary of Clinical Pharmacology Findings

In support of Procysbi, for the cystine concentration in white blood cell lysates, cystine was measured by a validated high-performance liquid chromatography coupled with tandem mass spectrometry method while total protein content in WBC lysates was assayed by bicinchoninic acid (BCA) method.

In this submission the same methods were used for both Procysbi and Cystagon throughout the clinical trials; therefore, the assessment of WBC cystine control by Procysbi in comparison to that by Cystagon in this 505(b)(2) application is not critically impacted by assay methods that are

[1] American Academy of Pediatrics, The use and misuse of fruit juice in pediatrics (2011), Pediatrics, 107(5), 1210-1213

different from historically used methods. In addition, a decrease in WBC cystine concentrations over a period of Procysbi treatment after switching from Cystagon in patients aged 2-5 years old was observed supporting the efficacy of Procysbi in this age group. However for treatment-naïve patients, the WBC cystine concentrations should be monitored using the reference range established by the assay methods to be used at a local laboratory. As such the labeling should include assay methods used in the clinical trials and have languages to recommend that the prescribers should consult local laboratories as WBC cystine concentrations are dependent on assay methods for cystine as well as total protein content of WBC lysates.

Summary of the sponsor's amendment related information

During the screening for patient enrollment, the sponsor noted WBC cystine concentrations for some patients whose WBC cystine concentrations had been under control by treating physicians. The sponsor stated that for patients in the U.S., a laboratory at (b) (4) has been the central laboratory for WBC cystine assay. Therefore the sponsor compared cystine concentrations and total protein in WBC lysate obtained at their analytical site to those from the (b) (4) laboratories. In their assessment, the sponsor found that total protein contents obtained by bicinchoninic acid (BCA) method were consistently lower than those by Lowry method[2,4], the method used at (b) (4) laboratory Therefore a correction factor for total protein content was applied to the final WBC cystine concentrations. See the Clinical Pharmacology Review dated 6/29/15 for more details.

The sponsor alluded that values for cystine concentrations were similar to those obtained by the (b) (4) laboratory. However the sponsor did not specify which method was used for cystine at the (b) (4) laboratory. The sponsor analyzed the quality control samples for WBC cystine provided by the (b) (4) for evaluation and improvement of screening, Diagnosis and treatment of Inherited disorders of Metabolism (ERNDIM)[3] using their LC/MS-MS method and found that the results were comparable to those by other laboratory using LC/MS-MS[4].

On the other hand, it was noted that early investigations on WBC cystine concentrations in patients with cystinosis and in healthy subjects were done using the cystine binding protein (CBP) assay[5][6] and the CBP assay has been the reference method. A formal comparison between

[2] Addendum to Validation for relative quantitation of total protein from human white blood cell (WBC) lysate by the Lowry method: (b) (4) Report Number: 1000-111640-2 dated April 26, 2013

(b) (4)

Bioanalytical Investigation Report #BR 2011-001" Investigation of a method used for the determination of cystine in white blood cell lysate (WBC) for Study RP 103-03

[5] Gahl, W. et al.,(2002) Cystinosis, N. Engl. J.Med. 347(2):111

[6] Oshima RG, Willis RC, Furlong CE, Schneider JA (1974) The utilization of a cystine binding protein from Escherichia coli for the determination of acid-soluble cystine in small physiological samples. J. Biol. Chem. 249:6033-9

cysteine protein binding assay and LC/MS-MS for cystine assay was not performed in this development program while generally good correlation between cystine measured with assays using LC/MS-MS and those obtained using the cystine-binding protein assay were reported by other published studies [7,8].

On June 25, 2015 the Agency requested clarifications on whether the reference range was established with the bioanalytical assay methods used in this development program.

In the response dated July 1, 2015, the sponsor clarified that the original method for cystine measurement was a cystine binding protein assay[9] at the (b) (4) laboratory until it was switched to new LC/MS-MS[10].

***Reviewer's comments***

As noted in the clinical pharmacology review dated 6/30/15, the treatment guideline does not specify the assay methods for the target WBC cystine. Initially a cystine-binding assay method was used for cystine concentration and assays such as amino acid chromatography or HPLC in addition to cysteine-binding assay also have been used[7]. Also different assay methods for total protein content such as modified Lowry method and bicinchoninic acid (BCA) method are being used while Lowry method has been used from the early studies for WBC cystine.

The variability of WBC cystine depends on variability of cystine assay and total protein assay as well as variability between laboratories. In addition with development of new analytical assay methods such as the method used in this program, WBC cystine can be measured as cystine without reduced to cysteine in which case the conversion of cystine concentration to half-cystine concentrations is unnecessary and can possibly introduce a calculation error. Therefore, the WBC cystine concentrations should be monitored using the reference range established by the assay methods to be used at a local laboratory in future trials.

[7] Chabli, A. et al., (2007) Measurement of cystine in granulocytes using liquid chromatography-tandem mass spectrometry, Clinical Biochemistry, 40 (9-10): 692-698

[8] García-Villoria, J. et al., (2012) Improvement of the cystine measurement in granulocytes by liquid chromatography-tandem mass spectrometry, Clinical Biochemistry 46: 271-274

[9] Smith, M. et al., (1987) Cystine: Binding Protein Assay, Methods in Enzymology 143 (23): 144

(b) (4)

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INSOOK KIM
07/17/2015

JUSTIN C EARP
07/17/2015

SUE CHIH H LEE
07/17/2015

EDWARD D BASHAW
07/17/2015
Concur with the need for the requested PMC.