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APPLICATION NUMBER:

207916Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA 207916 (SDN17)	Cetylev (Brand name)
Submission: 10/06/2015	Acetylcysteine (Generic name)
Reviewer	Elizabeth Y. Shang, Ph.D., R.Ph
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	DCP3
OND division	DGIEP
Sponsor	Arbor Pharmaceuticals LLC
Submission Type	NDA (505)(2)
Review Priority	Standard
Formulation; Strength(s)	Effervescent tablet; 0.5 gm and 2.5 gm

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed Section 12.3 of Cetylev. We found the labeling language in this section acceptable from an OCP standpoint. Labeling comments need to be conveyed to the sponsor.

1.2 Phase IV Commitments

None

1.3 Current Submission

Currently, Section 12.3 of acetylcysteine solution label contains information on [redacted] (b) (4). The original proposed

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label used [redacted] (b) (4) However, this information is not consistent with current labeling regulation and guidance. The Agency requested the sponsor use pharmacokinetic information obtained from dosing healthy subjects with Cetylev tablets in the bioequivalence (BE) study and published literature data on the ADME of acetylcysteine in humans to write this section. Refer to Information Request sent on 9/25/2015. The sponsor submitted new proposed language for Section 12.3 along with supporting references on 10/6/2015 (SDN17).

Labeling revisions are ongoing. Please refer to the final approved labeling when available. The following is the current revision of Section 12.3 with the reviewer's insertion in underlined red font and a single strikethrough for deletion.

12.3 Pharmacokinetics

[redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

Absorption

After administration of a single dose of CETYLEV Effervescent Tablets ~~(~~11 grams~~)~~ (dissolved in 300 mLs of water) to healthy adult subjects [redacted] (b) (4) (n=29), mean (CV%) Cmax was 26.5 ([redacted] (b) (4)) mcg/mL and mean (CV%) AUC_{inf} was 186 ([redacted] (b) (4)) hr•mcg/mL. Median (range) time to reach Cmax (Tmax) was 2 (1.0 to 3.5) hours.

[redacted] (b) (4)

Distribution

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The steady-state volume of distribution (Vd_{ss}) (b) (4) intravenous (b) (4) was (b) (4) 0.47 L/kg. The protein binding for acetylcysteine was 66 to 87%. (b) (4)

Reviewer's comment: The published literature provided by the sponsor for Distribution included an article by Olsson et al., 1988 reporting the Vd of 0.47 L/kg, which is used in the section of Distribution of Acetadote Injection label. Thus, the section of Distribution in the CETYLEV label is revised to be consistent with Acetadote Injection label. In sponsor submitted additional literatures data indicating that the protein binding ranges from 66% to 87%, consistent with the mean value of 83% reported in Acetadote IV label

Elimination

Metabolism

Acetylcysteine (i.e., *N*-acetylcysteine) undergoes extensive first pass metabolism and is postulated to form cysteine and disulfides (b) (4) (-*N,N*-diacetylcystine and *N*-acetylcystine). Cysteine - (b) (4) -is further metabolized (b) (4) -to form glutathione (b) (4) and -other metabolites.

Reviewer's comment: Several literature (Olsson B et al. 1988, Borgstrom et al. 1986 and Holdiness 1991) concluded that acetylcysteine undergoes extensive first pass metabolism. The postulated metabolism pathway illustrated by Holdiness in 1991 is shown below.

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Fig. 2. Proposed metabolic pathway of *N*-acetylcysteine (after DeCaro et al. 1989).

Excretion

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After a single oral dose of [^{35}S]-acetylcysteine 100 mg, between 13-38% of the total radioactivity administered was recovered in urine within 24 hours. In a separate study, (b) (4) -renal clearance was approximately 30% of total body clearance.

In healthy subjects (b) (4) given a single oral CETYLEV dose of 11 grams the mean (CV%) terminal plasma half-life was 18.1 ((b) (4)%) hours.

Specific Populations

Reviewer's comments: The sponsor also needs to provide updates on whether there are PK differences between sexes and in geriatric patients.

Hepatic Impairment

Following (b) (4) a (b) (4) intravenous 600 mg dose of acetylcysteine (b) (4) subjects with mild (Child-Pugh Class A; n=1), moderate (Child-Pugh Class B; n=4), (b) (4) or severe Child-Pugh Class C; n=4) hepatic impairment (b) (4) -and 6 healthy matched controls, mean T1/2 increased by 80%. The mean CL decreased by 30% compared to subjects with normal hepatic function (n=6). Systemic (b) (4) -acetylcysteine exposure (mean AUC) increased 1.6-fold in (b) (4) with hepatic impairment compared to subjects with normal hepatic function. These changes are not considered to be clinically meaningful.

Reviewer's comments: The changes in this section are mainly editorial. The hepatic impairment study reported in the label is the same as Acetylcysteine IV label.

Renal Impairment

Hemodialysis may move some (b) (4) of total acetylcysteine. (b) (4)

Reviewer's comments: (b) (4)

(b) (4)

(b) (4)

Reviewer's comments: (b) (4)

(b) (4)

Reviewer's comment: (b) (4)

2 References

2.1 References submitted by the current sponsor

Ref	Comments
1	Olsson B et al, Pharmacokinetics and Bioavailability of Reduced and Oxidized N-Acetylcysteine. *Eur J Clin Pharmacol*, 1988;34:77-82
2	The plasma concentration-time curve plot derives from plasma concentration and time data in Table 1 on page 16 of the Pharmacokinetic Report located in Appendix 16.1.12 of the AR10.001 study report. Mean PK parameter data are from Table 2 on page 18 of the Pharmacokinetic Report located in Appendix 16.1.12 of the AR10.001 study report.
3	De Caro L, et al, Pharmacokinetics and bioavailabilty of oral acetylcysteine in healthy volunteers. Arzheim-Forsch/Drug Res, 1989;39:382-386.
4	Borgstrom L, et al, Pharmacokinetics of N-acetylcysteine in man. *Eur J Clin Pharmacol*, 1986; 31: 217-222.
5	Rodenstein D, et al. Pharmacokinetics of oral acetylcysteine: absorption, binding and metabolism in patients with respiratory disorders. *Clinical Pharmacokinetics*, 1978; 3: 247-254. See Table II on page 250.
6	Brown M et al. Pharmacokinetics of intravenous *N*-acetylcysteine in men at rest and duringexercise. *Eur J Clin Pharmacol*, 2004; 60: 717-723.
7	Borgstrom L et al. Dose dependent pharmacokinetics of *N*-acetylcysteine after oral dosing toman. *Biopharmaceutics & Drug Disposition*, 1990; 1: 131-136. See Table 1 on page 133.
8	Holdiness MR. Clinical pharmacokinetics of *N*-acetylcysteine. *Clin Pharmacokinetics*, 1991; 20: 123-134.
9	Soldini D et al. Pharmacokinetics of *N*-acetylcysteine following repeated intravenous infusion in hemodialysis patients. *Eur J Clin Pharmacol*, 2005; 60: 859-864.
10	Hernandez SH et al. Pharmacokinetics of N-acetylcysteine during renal replacement therapies (RRTs). *Clinical Toxicology*, 2013; 51: 579
11	Jones Al, Jarvie DR, Simpson D, Hayes PC, Prescott LF. Pharmacokinetics of *N*-acetylcysteine are altered in patients with chronic liver disease. *Aliment Pharmacol Ther*, 1997; 11: 787-791.
12	Prescott LF, Donovan JW, Jarvie DR, Proudfoot AT. The disposition and kinetics of intravenous N-acetylcysteine in patients with paracetamol overdosage. *Eur J Clin Pharmacol*, 1989; 37: 501-506.
13	Paulsen O, Borgström L, Kagedal B, Walder M. No effect of oral N-acetylcysteine on the bioavailability of erythromycin and bacampicillin. *Eur Respir J*, 1988; 1: 171-5.
14	Tenenbein PK, Sitar DS, Tenenbein M. Interaction between N-acetylcysteine and activated charcoal: implications for the treatment of acetaminophen poisoning. *Pharmacotherapy*, 2001; 21: 1331-1336.
15	Rybolt TR, Burrell DE, Shults JM, Kelley AK. In vitro coadsorption of acetaminophen and N-acetylcysteine onto activated carbon powder. *J Pharm Sci*, 1986; 75: 904-906.
16	Rodenstein et al, Clinical Pharmacokinetics, 1978; 3: 247-2542 The article reported that protein binding was 83%.

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2.2 References submitted in NDA 21539 S-04 SLR (Acetadote Injection) to support PK/Biopharm (for internal use)

1. Ahola T, Fellman V, Laaksonen R, et al. Pharmacokinetics of intravenous N-acetylcysteine in pre-term new-born infants. Eur J Clin Pham 1999;55:645-50.

2. Beckett GJ, Donovan JW, Hussey AJ, Proudfoot AT, Prescott LF. Intravenous Nacetylcysteine, hepatotoxicity and plasma glutathione S-transferase in patients with paracetamol overdosage. Hum Exp Toxicol 1990;9(3): 183-6.

3. Boesgaard S, Iverson HK, Wroblewski H, et al. Altered peripheral vasodilator profile of nitroglycerin during long-term infusion of N-acetylcysteine. J Amer College Cardio 1994;23:163-9.

4. Borgstrom L, Kagedal B, Paulsen O. Pharmacokinetics of N-acetylcysteine in man. Eur J Clin Pharmacol 1986:31(2):217-22.

5. Borgstrom L, Kagedal B. Dose dependent pharmacokinetics of N-acetylcysteine after oral dosing to man. Biopharm Drug Dispos 1990;11:131-36.

6. DeCaro L, Ghizzi A, Costa R, et al. Pharmacokinetics and Bioavailability of oral acetylcysteine in healthy volunteers. Arzneimittel forschung 1989;39:382-6.

7. Holdiness MR. Clinical pharmacokinetics of N-acetylcysteine. Clin Pharmacokinet 991:20(2):123-34.

8. Horowitz JD, Henry CA, Syrjanen ML, et al. Combined use of nitroglycerin and Nacetylcysteine in the management of unstable angina pectoris. Circulation 1988;77:787-94.

9. Horowitz RS, Dart RC, Jarvie DR, Bearer CF, Gupta U. Placental transfer of N-acetylcysteine following human maternal acetaminophen toxicity. J Toxicol Clin Toxicol 1997;35(5):447-51.

10. Jones AL, Jarvie DR, Simpson D, Hayes PC, Prescott LF. Pharmacokinetics of N-acetylcysteine are altered in patients with chronic liver disease. Aliment Pharmacol Ther 1997;11:787-91.

11. Lewis PA, Woodward AJ, Maddock J, High performance liquid chromatographic assay for N-acetylcysteine in plasma and urine. J Pharm Sci 1984:73:996-8.

12. Olsson B, Johansson M, Gabrielsson J, Bolme P. Pharmacokinetics and bioavailability of reduced and oxidized N-acetylcysteine. Eur J Clin Pharmacol 1988;34(1):77-82.

13. Prescott LF, Donovan JW, Jarvie DR, Proudfoot AT. The disposition and kinetics of intravenous N-acetylcysteine in patients with paracetamol overdosage. Eur J Clin Pharmacol 1989;37:501-06.

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14. Rodenstein D, De Coster A, Gazzaniga A. Pharmacokinetics of oral acetylcysteine: absorption, binding and metabolism in patients with respiratory disorders. Clinical Pharmacokinetics 1978;3:247-54.

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/s/

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01/05/2016

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