APPLICATION NUMBER:

207916Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)
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 (b)(4). The original proposed
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

**Absorption**

After administration of a single dose of CETYLEV Effervescent Tablets (111 grams) (dissolved in 300 mLs of water) to healthy adult subjects (n=29), mean (CV%) Cmax was 26.5 mcg/mL and mean (CV%) AUC$_{inf}$ was 186 hr*mcg/mL. Median (range) time to reach Cmax ($T_{max}$) was 2 (1.0 to 3.5) hours.

**Distribution**
The steady-state volume of distribution (Vdss) intravenous was 0.47 L/kg. The protein binding for acetylcysteine was 66 to 87%.

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 (N,N-diacetylcysteine and N-acetylcysteine). Cysteine is further metabolized to form glutathione 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.

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

Excretion
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, renal clearance was approximately 30% of total body clearance.

In healthy subjects, given a single oral CETYLEV dose of 11 grams the mean (CV%) terminal plasma half-life was 18.12 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 a 600 mg dose of acetylcysteine intravenous dose of subjects with mild (Child-Pugh Class A; n=1), moderate (Child-Pugh Class B; n=4), or severe (Child-Pugh Class C; n=4) hepatic impairment 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 acetylcysteine exposure (mean AUC) increased 1.6-fold in subjects 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 of total acetylcysteine.

Reviewer’s comments:
2 References

2.1 References submitted by the current sponsor

<table>
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<tr>
<th>Ref</th>
<th>Comments</th>
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<tbody>
<tr>
<td>2</td>
<td>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.</td>
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<tr>
<td>7</td>
<td>Borgstrom L et al. Dose dependent pharmacokinetics of N-acetylcysteine after oral dosing toman. <em>Biopharmaceutics &amp; Drug Disposition</em>, 1990; 1: 131-136. See Table 1 on page 133.</td>
</tr>
<tr>
<td>10</td>
<td>Hernandez SH et al. Pharmacokinetics of N-acetylcysteine during renal replacement therapies (RRTs). <em>Clinical Toxicology</em>, 2013; 51: 579</td>
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<tr>
<td>16</td>
<td>Rodenstein et al, Clinical Pharmacokinetics, 1978; 3: 247-2542</td>
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</tbody>
</table>

The article reported that protein binding was 83%.
2.2 References submitted in NDA 21539 S-04 SLR (Acetadote Injection) to support PK/Biopharm (for internal use)


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/s/

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01/05/2016

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01/05/2016