CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-539

MEDICAL REVIEW

Center for Drug Evaluation and Research

Office of Drug Evaluation III

Division of Gastrointestinal and Coagulation Drug Products

MEDICAL OFFICER REVIEW

NDA: 21-539/NOOO/BZ

Sponsor: Cumberland Pharmaceutical, Inc

Drug: Acetadote® (acetylcysteine injection)

Indication: Antidote against Acetaminophen hepatotoxicity

Document: Response to Non-Approvable Letter

Date the Document was Received by CDER: July 24, 2003

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Date Review Finalized:

Medical Officer: Robert Prizont, MD

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

I recommend approval of ACETADOTE®, an intravenous formulation of N-acetylcysteine,

As stated in the last section of the Clinical Review, I recommend inclusion in the label of the following: (1)

and (2) a WARNING stating that serious anaphylactoid reactions, including death, in patients with asthma

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

None.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Cumberland Pharmaceuticals first submitted this NDA on July 1, 2002. As support of efficacy, the submission included five historical references on the use of N-acetylcysteine (NAC), and an Interim Analysis (IA) of a study (CMAX CM8801), conducted in Australia to assess tolerance of two intravenous (i.v.) loading regimens of NAC (*150 mg/k administered in 15 min or in a 60 min infusion, and a maintenance dose of 300 mg/k for 20 h*). Efficacy of NAC as antidote of an acetaminophen overdose was defined as serum liver transaminases (*ALT/AST*) below 1000 IU/L. None of the studies included a comparison control treatment, and only a few of the historical references studied efficacy of NAC as antidote to acetaminophen overdose. Further, a comprehensive meta-analysis published in 1999, integrating studies with i.v. and oral NAC in acetaminophen overdose, was not included in the submission. The application was rendered non-approvable. The non-approvable letter

included a recommendation [redacted]

In this submission, Cumberland Pharmaceuticals included results of its meta-analysis, the CM8801 data, and results from the Hunter Area Toxicology Service (HATS), based in Newcastle, Australia.

B. Efficacy

Cumberland's meta-analysis comprised 456 published references with a total of 10,818 patients, of which 3,079 had acceptable information on efficacy. Due to the heterogeneity of gathered references, the meta-analysis was divided in three databases, i.e. Case-Report Database, Patient Database, and Group Database. The Case-Report Database included 30 case-report references and 33 acetaminophen patients treated with NAC (13 treated by the i.v. route, 15 treated by the oral route, 5 treated by combined routes). By all routes of administration, early NAC treatment (within 8 h from overdose) resulted in prevention of hepatotoxicity (*hepatotoxicity developed in 1/13 patients of the i.v. group, 0/15 patients of the oral group, 1/5 patients of the combined route group*). Conclusions from this database, however, are of little or no value, for (a) the cited 30 references of the database were not identifiable and, (b) number of patients was too small to attain statistical significance. The Patient-Database was taken from 13 references encompassing 97 acetaminophen-overdosed patients; 85 treated by i.v. NAC and 12 treated by oral NAC. This database also showed efficacy with early (within 10 h from overdose) NAC treatment (*hepatotoxicity developed in 3/85 patients of the i.v. group*). This database suffered of similar deficiencies as the previous one, namely, no information on the source of references, and number of patients comprising the oral group were too small to arrive at any conclusion. The Group-Database was the largest, i.e., 2808 acetaminophen-overdosed patients treated with NAC. It included seven identifiable references. This Group-Database also showed superior efficacy with early NAC treatment (*hepatotoxicity developed in 5% of patients treated with i.v. NAC, and 7% of patients treated with oral NAC*), than with late NAC treatment. However, and as pointed out by the statistician reviewer, the studies could not be statistically *integrated* because either patients belonged to a special population (*pregnant*

women in one study), objectives were different, or the treatment regimen differed from the one proposed by Cumberland, e.g., in one study a small group of patients were solely treated with activated charcoal (*study by Buckley et al, Clinical Toxicology, 37:759-767,1999*). This Australian 1999 study by Buckley et al, included a historical meta-analysis. In the Buckley meta-analysis, there were three studies, totaling 226 patients, reporting treatment with i.v. NAC 300 mg/k for 20 h (the i.v. regimen proposed by the sponsor), and three other studies, totaling 1710 patients, reporting treatment with the approved oral NAC dose of 1300 mg/k for 72 h (*see Table 3, Efficacy Conclusions section of this review*). The majority of the studies included in the Buckley meta-analysis showed that early administration of i.v. or oral NAC treatment (<10 h from overdose) resulted in a low hepatotoxicity incidence (2% to 16%).

HATS, a 12 year observational study conducted in Newcastle, Australia, included 1749 admissions for acetaminophen overdose; 350 with available serum liver transaminases, of which 208 were treated with intravenous NAC. As in previous databases, early administration of i.v. NAC resulted in a low incidence of hepatotoxicity (3%). HATS included a no-treatment comparison of 72 patients (17% developed hepatotoxicity), and a group of 70 patients treated with alternative treatments to NAC, i.e., gastric lavage or activated charcoal (3% hepatotoxicity).

The CMAX CM8801 was terminated with an enrollment of 223 patients. 177 had available serum ALT levels. Of the 177 patients with available ALTs, 56 received early NAC treatment. None of these 56 patients developed hepatotoxicity. Hepatotoxicity was observed in six of the remaining 108 patients. As mentioned, this CMAX CM8801 was primarily designed to assess tolerance and safety of two intravenous NAC loading regimens. Assessment of efficacy was a secondary evaluation. Hence, the efficacy results from this safety study are of limited significance.

Based on the efficacy results from the large Buckley study/meta-analysis the HATS observational data, and the additional supportive clinical information provided by the Group-Database, I conclude that there is substantial efficacy data to support the approval of Cumberland's NAC intravenous formulation for treatment of acetaminophen overdose if used during the early 8-10 h from the overdose.

C. Safety

This synopsis supplements the safety included in my first review (*see Executive Summary, Page 8, December 2002 MO review*). I then reported 22 deaths in patients treated with i.v. NAC. In many of those cases, fatal outcomes were due to administration of excessive NAC

I. Introduction and Background

a. In the 1970's and 1980's, mortality from acetaminophen [*acetyl-para-aminophenol (APAP)*] overdose was higher than 30%. APAP is a chemical compound marketed OTC as oral tablets or caplets for relief of pain (*Tylenol, McNeil Lab, PA*). In the liver, APAP is metabolized by the CYP oxidizing system into a harmful metabolite, i.e. N-acetyl-benzoquinone amide (*NAPQI*). H^+ donors such as glutathione detoxify NAPQI into harmless mercapturic acid metabolites. However, if ingested in large quantities, e.g. >3 g, the reserve of glutathione is depleted, and the liver is unable to detoxify the excess of APAP. As a consequence, liver necrosis and failure may ensue. N-acetylcysteine (*NAC*) belongs to the class of drugs known as sulphydryl agents. As reducing agents, this class of drugs prevent cell oxidation and cell death, by acting as cytoprotective H^+ donors. When administered, NAC behaves as a glutathione substitute. In 1984, this Agency approved an oral formulation (*Mucomyst, Mead Johnson, co-sponsored by McNeal Lab)* as antidote for APAP overdose. **The approved treatment included gastric lavage, oral administration of activated charcoal, followed by 1330 mg/kg of Mucomyst given for over 72 hours. The most common oral regimen is a 72 h protocol consisting of a 140 mg/k loading dose and 17 subsequent 70 mg/k doses administered every 4h.**

Intravenous formulations of NAC are approved in the United Kingdom, Germany, France, Italy, Australia, New Zealand and Canada.

b. Cumberland Pharm. submitted this NDA on July 1, 2002. After completion of the review process, the Division concluded that there was no substantial evidence from adequate and well-controlled trials that Acetadote® will have the effect it purports to have under the conditions of use described in its proposed labeling. The proposed label stated that Acetadote® was *indicated for intravenous treatment* [redacted] **The label recommendations for Acetadote® Dose and Regimens of administration included an intravenous (i.v.) loading dose of 150 mg/kg in 200 ml of 5% dextrose, infused for** [redacted] **, and an i.v. maintenance dose of 50 mg/kg in 500 ml of dextrose, infused for 4 hours, followed by 100 mg/kg in 1000 ml 5% dextrose infused over 16 hours.** In my MO review of December 16, 2002, I analyzed and commented on the interim analysis of CMAX study CM8801, designed to assess safety of NAC i.v. bolus or continuous infusion in APAP overdose, and on the five historical studies[1,2,3,4,5] submitted by Cumberland Pharm to support approval for the proposed indication, dosage and regimen of administration. I concluded that though the safety of NAC i.v. administration appeared acceptable, the efficacy of Acetadote could not be supported by the submitted historical studies. Only three of the submitted studies used i.v. NAC as antidote of APAP overdose, they were open-label, and none included a comparison control treatment. Furthermore, the studies revealed variable NAC

efficacy, and of relevance, none of the studies used the intravenous dosing regimen proposed in the label.

Based on the deficiencies, I recommended (1) a non approvable regulatory action, (2)

recommendations to be conveyed to Cumberland, included

In a letter to Cumberland dated December 30, 2002, the Division conveyed to the NDA sponsor the non-approvable (*NA*) decision,

Reference List of Supporting Historical Reports

1. *Keays R et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 303:1926-1929, 1991.*
2. *Perry HE et al. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label clinical trial. J Pediatr 132:149-152, 1998.*
3. *Smilkstein MJ et al. Acetaminophen overdose: a 48 h intravenous N-acetylcysteine treatment protocol. Ann Emerg Med 20:1058-1063, 1991.*
4. *Oh TE and GM Shenfield. Intravenous N-acetylcysteine for paracetamol poisoning. Med J Aust 1:664-665, 1980.*
5. *PrescottLF. Treatment of severe acetaminophen poisoning with intravenous acetylcysteine. Ann Intern Med 141:386-389, 1981.*

II. Chemistry, Biopharmacology, Statistical Issues.

The sponsor has addressed chemistry issues. Biopharmacology of i.v. NAC was considered acceptable in the first submission. The statistical review is ongoing. , Whenever required, sections of this clinical review will include comments on different statistical issues.

III. Response from Cumberland to the Clinical Issues in the NA Letter.

In response to the recommended clinical alternatives, i.e., [redacted]

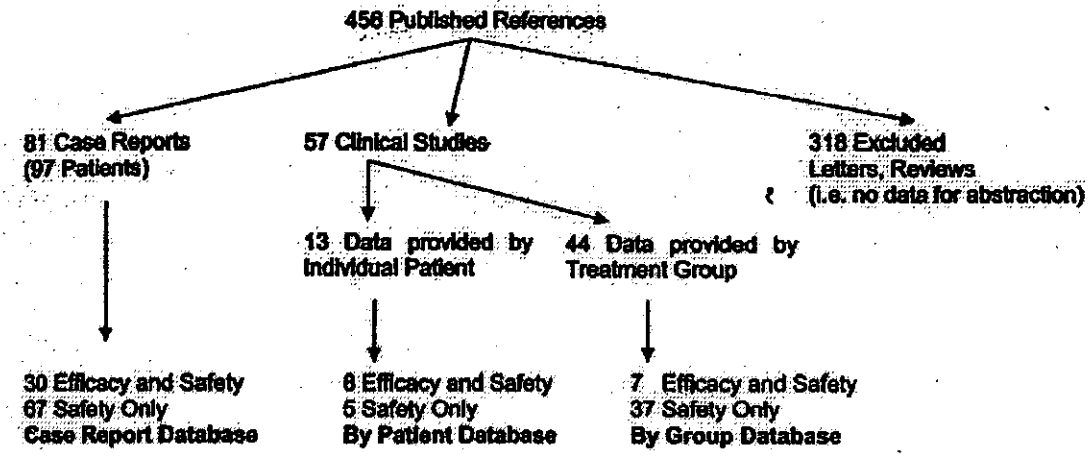
Cumberland chose to assess comparability between the i.v. and oral NAC routes, by performing of meta-analysis of the literature. Cumberland also submitted observational data from the Australian Hunter Area Toxicology Service (HATS), and the completed data from the reported CMAX Study No CM8801..

A. Review of Efficacy

Cumberland's Meta-Analysis.

Cumberland search for worldwide acetaminophen literature relied primarily on a database maintained by the Rocky Mountain Poison and Drug Center (RMPDC) This database was subsequently updated using the terms *acetylcysteine* and *acute toxicity* through January 31, 2003, with a Medline and Embase search. The combined search returned *456 English published references* encompassing case reports, studies, and reviews. The 456 references reported a totals of 10, 818 patients . The 10,818 patients qualify for safety analysis, but only 3079 patients had enough information on efficacy to qualify for efficacy analysis. Furthermore, the heterogeneity of the database, e.g. individual case reports, letters of cases, prospective and retrospective studies, required a separation of datasets. According to these criteria, Cumberland created 3 databases; namely *(1) Case Report Database, (2) Patient Database, and (3) Group Database.* The three groups depicted in this next Cumberland schematic (*Page 40, Vol. 1*).

Figure 2. Schematic of Published Literature Identified for the Meta-Analysis



The grouped data sets included demographic variables, e.g., age, gender, race, total amount of NAC administered, activated charcoal administered, co-poisoning, treatment of activated charcoal administration. The primary efficacy endpoint in APAP OD is the development of liver failure, manifested by ALT and AST serum levels > 1000 IU/L.

Treatment groups within studies were selected for efficacy analysis if they met the following four criteria:

- Patients must have a APAP serum level above the considered a toxic range, i.e. 150 g/ml according to customarily used normogram (Rumack-Matthew).
- Route of NAC administration specified (oral or i.v.)
- Time from APAP ingestion to NAC treatment specified
- The peak AST and/or ALT levels or the number of patients who experienced an AST and/or ALT >1000 IU/L must have been reported.

Cumberland notes that since 1973 when it was demonstrated that acetaminophen liver damage could be protected by administration of SH donors such as NAC, most of the studies compared NAC to other "*supportive therapy*", and not to placebo. Some published studies compared oral versus i.v. NAC. Studies also have shown that NAC therapy is more effective if administered 8-10 hours after the initial APAP OD. This is the time-interval before oxidized APAP metabolites like NAPQI damage the liver. Yet, in most studies, the largest proportion of patients seek medical assistance after the 8-10 h initial period. Analyses performed by the sponsor include comparisons of efficacy between "*early*" (8-10 h) and "*late*" (post 10 h) APAP overdose.

1. Case Report Database.

a. Demographics and Ingestion-to-Treatment Interval.

The group included 81 case report references describing a total of 97 patients. According to the sponsor's criteria, of the 97 patients described in these case reports, only 30 met the criteria necessary for efficacy analysis.

The mean age of the 97 patients was 25 y (1 day to 84 y); 70% were females. Race information was available in 18 patients (14 White, 3 Hispanic, 1 Black).

Ingestion-to-Treatment (ITT) interval was known in 62 patients (64%). Of the 62 patients in whom the ITT was known, 26 (42 %) were treated within 10 hours; 36 (58%) were treated beyond the 10 h early period.

12 patients had abused alcohol at the time of the APAP OD, and 36 had ingested potential confounding toxic drugs such as anti-depressants or tranquilizers.

b. Dosage.

The sponsor text (Page 26, Vol 1) stated that total amount of NAC administered was reported in 22 patients (22/97 = 23%). *Of the 22 patients in whom the total NAC dose was known, 9 received 1330 mg/k, which is the dose approved for the oral route, and 7 patients were given 300 mg/k, the dose customarily delivered by the i.v. route.* The references selected by the sponsor reported 21 patients receiving charcoal treatment.

c. Efficacy.

Efficacy was assessed in the 33 patients that met the four aforementioned pre-established criteria to evaluate efficacy. The following Cumberland Table 4 illustrates the results of the primary efficacy based on the pre-established endpoint, i.e., prevent biochemical liver failure as shown by serum ALT or AST levels >1000 IU/L, and, pre-established criteria required to assess efficacy.

Table 4. Number of Patients Developing Hepatotoxicity based on early or late administration of NAC by the oral or intravenous route, Case Reports

	Intravenous NAC Only		Oral NAC Only		Both (Oral and IV)[1]	
	Early (≤8 hrs)	Late (>8 hrs)	Early (≤8 hrs)	Late (>8 hrs)	Early (≤8 hrs)	Late (>8 hrs)
No Hepatotoxicity Developed (ALT/AST <150 U/L)	1	4	2	3	1	2
Mild Hepatotoxicity Developed (ALT/AST 150-1000 U/L)	0	4	1	1	1	0
Severe Hepatotoxicity Developed (ALT/AST >1000 U/L)	1	3	0	8	1	0

[1] Patients who received both oral and IV NAC treatment

The following Cumberland Table 13.1.5.4 depicts the statistics of patients developing hepatotoxicity, ALT/AST >1000 IU/L, in the oral versus i.v. route, regardless of the ITT interval.

ORAL vs. IV

	ALT/AST>1000 IU/L	ALT/AST<=1000 IU/L	Proportion with ALT/AST>1000 IU/L
Oral	6	4	0.60
IV	5	10	0.33

Chi-Square Statistic p-value=0.188 (less than 40% power)
Relative risk 1.8 (confidence limits 0.75-4.32)
Power Calculation 20-40%

Cumberland concluded that "*this population is not large enough to statistically compare the efficacy between oral NAC and i.v. NAC and between early and late treatment groups (power,50%)*". Cumberland noted that in the overall 41 patients in whom ITT interval was known there was a trend towards less hepatotoxicity in the early treatment group.

Reviewer Comments.

I concur with the sponsor's conclusion that the population is not large enough to show statistical superiority in efficacy, but I disagree that there is any concluding trend shown in these results. A relevant issue is the lack of information about the 30 patients selected to assess efficacy. Neither the text nor the submitted references (Appendix A, Vol. 2), include demographic characteristics and immediate medical history of the selected patients. The lack of this information hampers any inference about a potential efficacy of this patient population.

2. Patient Database

a. Patient Disposition and Demographics.

According to the sponsor, this database included 57 "*clinical study/trial*" references. Of these, 13 references provide data on an "*individual patient base and 44 provide data based on a treatment group descriptions*". Of the 13 references that provided data on an individual patient bases, 8 references, encompassing 97 patients, were selected by Cumberland to demonstrate efficacy in this Patient Database.

Of the 97 patients, 36 were females (37%), 24 males (25%) and 37 (38%) unknown. Age was known in 60 patients; mean age was 27 y (1-68 y). Eighty five patients (88%) were treated with intravenous NAC, and only 12 (12%) with oral NAC. Of these 97 NAC treated patients, 59 (61%) received 300 mg/k, 6 (6%) received 250 mg/k, and 9 (9%) received a dose of 1330 mg/k.. The NAC dose was unknown in 23 patients (*Cumberland reminds that oral NAC dose is 1330 mg/k whereas the standard i.v. dose is 300 mg/k*). Concomitant use of charcoal was given to 6 of the 97 patients.

b. Efficacy.

Cumberland Table 10 (Page 59, Vol. 1) shows the overall primary efficacy with NAC treatment, i.e., prevention of serum liver transaminases >1000 IU/L. As stated, only 12% of this patient population were administered oral NAC, while 88% of the patients were treated with intravenous NAC. Cumberland Table 10 (Page 59, Vol. 1) shows that 24% (20/85) of patients given i.v. NAC

developed hepatotoxicity whereas 76% (65/85) did not. Among the 12 patients who received oral NAC, 4 had serum liver transaminases >1000 IU/L. These results revealed no statistical difference between i.v. NAC and oral NAC in the incidence of hepatotoxicity. (Chi-Square p=0.461).

Table 10. Number of Patients Developing Hepatotoxicity When Administered Oral vs. IV NAC, Studies, Data by Patient

		Hepatotoxicity ALT/AST >1000	No Hepatotoxicity ALT/AST ≤1000
Oral Administration N=12	N	4	8
	%	33.33%	66.67%
IV Administration N=85	N	20	65
	%	23.53%	76.47%

Cumberland Table 11 (Page 34, Vol. 1), shows the number of patients with hepatotoxicity in patients treated within 10 hours of the APAP OD with i.v. or oral NAC (early treatment). Noticeable, is the *single oral* NAC patient treated <10 hours of the APAP OD. There were no patients treated within 8 h with oral NAC.

Table 11. Number of Patients Developing Hepatotoxicity When Administered Oral or IV NAC Early (≤10 hours) or Late (>10 hours), Studies, Data by Patient

			Hepatotoxicity ALT/AST >1000	No Hepatotoxicity ALT/AST ≤1000
Oral Administration	Late (>10 hrs) N=11	N	4	7
		%	36.36%	63.64%
	Early (≤10 hrs) N=1	N	0	1
		%	0.00%	100.00%
IV Administration	Late (>10 hrs) N=35	N	17	18
		%	48.57%	51.43%
	Early (≤10 hrs) N=50	N	3	47
		%	6.00%	94.00%

Cumberland Table 7 (Page 32, Vol. 1) illustrates the mean ALT/AST in patients who received early or late i.v. NAC treatment. As seen, there was a large variation from the mean.

Table 7. Mean ALT/AST for Patients Receiving Early (≤8 hrs) or Late (>8 hrs) IV NAC treatment, Studies, Data by Patient.

		N	Mean	Std. Deviation
Early NAC Treatment	Peak ALT	36	156	542
	Peak AST	12	249	715
Late NAC Treatment	Peak ALT	23	3570	5213
	Peak AST	29	2375	3367

Cumberland concluded that i.v. NAC showed statistical superiority in reducing the incidence of hepatotoxicity when administered to patients within eight hours of acetaminophen injection (*compared to patients who had treatment after eight hours*). Cumberland noted that *no comparison can be made between oral and intravenous NAC based on ingestion to treatment interval, since there were no reported early treatment group patients for oral NAC group.* The sponsor added that *the oral late treatment group, although too small to statistically compare, had similar percentages of hepatotoxicity compared to the late intravenous group.*

Reviewer Comments.

The primary aim of the meta-analysis was to determine whether the proposed intravenous NAC formulation and approved oral formulation have comparable efficacy. This Patient Database group can not be used for the primary aim, due to the small number of patients treated with oral NAC, as acknowledged by the sponsor in its conclusion. Similarly, the absence of patients treated with oral NAC at the early phase of the NAC therapy, i.e., <10 h of APAP OD, precludes any conclusion of the benefit by an early NAC i.v. treatment.

Other deficiencies include the absence of information on the administered NAC dose in 24% of the patients and incomplete intravenous dosing in 6% of the patients. As in the previous database, Cumberland did not provide the list of the selected 13 references used to obtain the 97 patient database.

3. Group Database.

This search identified 57 clinical study/trial references. The sponsor reports that of these 57 clinical trial references, 44 provided treatment group descriptions, and seven references qualified for efficacy analysis. These references provided data on 2,808 patients.

a. Demographics

The following Cumberland Table 12, Page 62, Vol. 1, illustrates the seven selected references and the demographic from each study.

Table 12. Demographic and Treatment Information, Studies, Data by Group

	Bond, 1999	Buckley, 1999	Prescott, 1981	Rumack, 1981	Smilkstein, 1991	Smilkstein, 1988	Riggs, 1989
N, Treated with NAC	18	88	100	155	179	2248	24
Route of Administration	Oral	IV	IV	Oral	IV	Oral	Oral
% Female	NA	NA	NA	NA	67.6	69.2	100.00
NAC Regimen	1330 mg/kg oral, 72 hours	300 mg/kg IV, 20 hours	300 mg/kg IV, 20 hours	1330 mg/kg oral, 72 hours	980 mg/kg IV, 48 hours	1330 mg/kg oral, 72 hours	1330 mg/kg oral, 72 hours

The following Cumberland Table 14, Page 63, Vol 1, illustrates the number of patients who met the criteria of hepatotoxicity during oral or NAC treatments.

Table 14. Number of Patients Developing Hepatotoxicity When Administered Oral vs. IV NAC, Studies, Data by Group

		Hepatotoxicity ALT/AST >1000	No Hepatotoxicity ALT/AST <1000
Oral Administration N=2443	N	548	1895
	%	22.43%	77.57%
IV Administration N=365	N	56	309
	%	15.34%	84.66%

b. Efficacy

The following Cumberland Table 15, Page 64, Vol. 1, depicts the proportion of patients treated <10 h after the APAP OD and developed hepatotoxicity. The data shows significant difference in favor of early NAC treatment.

Table 15. Number of Patients Developing Hepatotoxicity When Administered Oral or IV NAC Early (<10 hours) or Late (>10 hours), Studies, Data by Group

			Hepatotoxicity ALT/AST >1000	No Hepatotoxicity ALT/AST <1000
Oral Administration	Late (>10 hrs) N=1630	N	494	1136
		%	30.31%	69.69%
	Early (≤10 hrs) N=813	N	54	759
		%	6.64%	93.36%
IV Administration	Late (>10 hrs) N=181	N	47	134
		%	25.97%	74.03%
	Early (≤10 hrs) N=184	N	9	175
		%	4.89%	95.11%

The sponsor concluded that the i.v. NAC group was better (50%) than the oral group, and, that early NAC treatment (<10 h) was significantly better than late NAC treatment (>10 h).

Reviewer Comments.

This database encompass the largest patient population. Unlike the previous two databases, where there was absence of information about the source of patient population, the references used to compile this Group-Database was identified by the sponsor. Since approvability of Cumberland's NAC i.v. formulation would rest, in part, on the soundness of the submitted meta-analysis, it is important to determine if the studies used to integrate this group database were statistically "combinable" (Egger M, GD Smith. Meta-analysis. Potentials and promise. BMJ, No 7119, Vol. 315, 1997, taken from http://bmj.mbjjournals.com/archive/7119/7119ed.httm*). According to the reviewer statistician, the Cumberland meta-analysis cannot be used as a means to determine efficacy, for the basic principles required to integrate the studies, i.e.., similar design, adequacy of trials, similar patient population, known route of drug administration, similar objectives/endpoints, were not fulfilled. The following were the reasons for the statistician's conclusion:*

- *Study Population. The study conducted by Riggs et al. focused largely on a "special" population, namely, pregnant women overdosed with APAP (Riggs BS et al. Acute acetaminophen overdose during pregnancy. Obstet Gynecol 74:247-253, 1989).*

- *Study Objectives. The objective of the Bond study was to estimate, retrospectively, the incidence rates of acetaminophen overdose in emergency evaluations and hospitalizations. Further, the report did not include the route used for NAC treatment. (Bond GR and Hite LD. Population-based incidence and outcome of acetaminophen poisoning by type of ingestion. Academ Emerg Med. 6:1115-1120, 1999).*

- *Dates of Treatment. Prescott did not describe the date of treatments with i.v. NAC. The statistician reviewer estimated that patients were treated between 1973 and 1981 (Prescott LF. Treatment of severe acetaminophen poisoning with intravenous acetylcysteine. Arch Intern Med. 141:386-389, 1981).*

- *Treatment Regimen. Buckley et al used an intravenous NAC treatment that differed from the one proposed by the applicant.. The author stated that management of patients presenting within 4 hours who have taken >125 mg/k of acetaminophen was to give activated charcoal (1-2 g/k) and intravenous fluids. Patients admitted within 8 hours of poisoning were given NAC if the acetaminophen*

concentration is in the probable or high risk range (Buckley et al. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen [paracetamol] poisoning? Clinical Toxicology, 37:759-767, 1999).

- *Intravenous NAC Regimen. .Smilkstein et al used an i.v. NAC regimen that differed from the proposed Cumberland regimen. Smilkstein et al gave a total intravenous dose of 980 mg/k over a period of 48 h whereas Cumberland proposes an intravenous dose of 300 mg/kg to be given in 21 h.(Smilkstein MJ et al. Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. Ann Emerg Med. 20:1058-1063, 1991).*

In spite of the deficiencies in the statistical methodology, the studies by Prescott and particularly the more recent study/meta-analysis by Buckley revealed clinical differences, i.e., lower serum ALT levels, in favor of the use of NAC treatment in patients who have APAP plasma levels in the toxic range, i.e., >200 mg/L, and more importantly, no differences in between the use of intravenous and oral NAC . These results are shown in the next Table 4, taken from the aforementioned Buckley et al meta-analysis..

Table 4

Pooled Proportions and 95% CI for Patients with Hepatotoxicity in Combined Probable and High Risk Groups Treated with NAC (Combining Results of IV Studies Using a Random Effects Model)

Treatment delay (hours)	Pooled IV NAC	Smilkstein 1988 (oral NAC)
0–8	1% (0–8)*	3% (2–6)
0–10	3% (0–6)	6% (4–8)
10–24	30% (5–55)	26% (24–29)
15/16–24	46% (10–82)	41% (35–47)‡
Total	16% (2–29)†	19% (17–21)

* Exact 95% CI based on grouped data.
† 18% (3–33%) if untreated patients with at risk concentrations (presenting late) from our series included.
‡ Reported high risk group only.

CMAX Report No CM6603. The Hunter Area Toxicology Service (HATS)

a. Study Design, Patient Population, Demographics.

This was an ongoing prospectively design, open-label-observational study conducted in the greater Newcastle area in New South Wales, Australia since

January 1987. The major hospitals involved are the .

The HATS database encompassed 1749 patients admitted for APAP overdose in a period of sixteen years, from January 1987 to January 1983. Of the 1749 APAP OD admissions, 399 (23%) received NAC treatment, while1350 were not administered NAC (77%). Of the 1350 who did not receive NAC treatment, 822 received some other treatment, such as gastric lavage, oral charcoal administration.

The age of patients ranged from 2 months to 96 years. The majority (77%) of patients who received NAC treatment ranged in age from 16 y to <40 y. Sixty five percent of patients were females.

Approximately 22-24% of patients took toxic co-poisons of relevance. The proportion was similar in the NAC treated or untreated patients. Approximately 17% were users of alcohol.

b. Efficacy.

As stated, 399 patients received NAC treatment. Of these 399 patients, 208 had serum liver transaminases (ALT or AST) measured during admission; 64 were treated within 8 h of APAP OD, 128 were treated after 8 h of admission, and in 16 patients the time after the OD was unknown.

Of the patients who received other treatments, i.e., gastric lavage, charcoal administration, 142 had serum liver transaminases measured during the admissions.

Table 10.4.3 summarizes the results of the three groups: NAC treated, treated but not with NAC, and untreated. As noticeable, 83% of patients treated within 8 hours of the APAP overdose had normal serum liver transaminases. This 83% compares with 60% of patients who received other treatments but no NAC, and 47% of patients who remained untreated. Patients who received NAC treatment after 8 h of the APAP overdose had a comparable proportion of normal serum transaminases than untreated patients. The proportion of patients with serum transaminases exhibiting hepatotoxicity, i.e., > 1000 U/L was very low in patients NAC treated within 8 h of the overdose and in patients treated with other treatments (3%) while relatively high in the untreated group (17%). Differences between the group who had NAC within 8 h, and those who received late NAC treatment, or remained untreated, was statistically significant, at a level below $p<0.01$.

Executive Summary Section

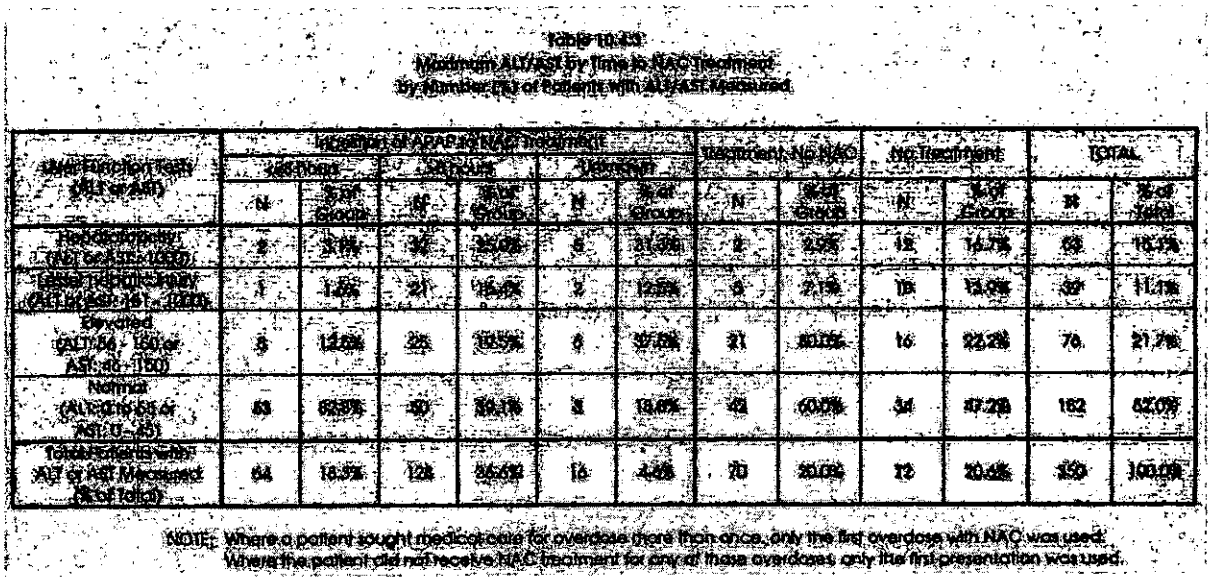


Table 10.13
Maximum ALT/AST by Time to NAC Treatment
by Number (%) of Patients with ALT/AST Measured

Max Function Test (ALT or AST)	Duration of APAP to NAC treatment						Treatment, No NAC		No Treatment		TOTAL	
	≤8 hours		>8-24 hours		Unknown							
	N	% of Group	N	% of Group	N	% of Group	N	% of Group	N	% of Group	N	% of Total
Hepatotoxicity (ALT or AST >1000)	2	3.1%	14	24.6%	5	31.3%	2	2.5%	15	16.7%	68	15.1%
Liver Hypofunction (ALT or AST >1000)	1	1.6%	21	16.4%	2	12.5%	3	7.1%	10	13.9%	37	11.1%
Elevated (ALT>84 - 1000 or AST>86 - 1000)	8	12.5%	25	19.5%	4	37.5%	21	30.0%	16	22.2%	76	21.7%
Normal (ALT<=84 or AST<=86)	53	82.8%	50	39.1%	3	18.8%	43	60.0%	34	47.2%	182	52.0%
Total Alerts with ALT or AST Measured (% of Total)	64	18.3%	128	36.6%	16	4.6%	70	20.0%	72	20.6%	350	100.0%

NOTE: Where a patient sought medical care for overdose more than once, only the first overdose with NAC was used. Where the patient did not receive NAC treatment for any of those overdoses, only the first presentation was used.

Reviewer Comments.

These observational data provide information on the superiority of NAC intravenous treatment versus no treatment. As in the previous comparisons, there was significantly lower hepatotoxicity in patients treated within eight hours after acetaminophen overdose. Noteworthy, during this early post-overdose period, gastric lavage and/or oral charcoal were as efficacious as NAC treatment. Absent in this observational data was a comparator of oral NAC treatment.

CMAX Study No CM8801.

Conducted in _____ and contracted by Cumberland, CMAX CM8801 was a trial designed to assess the safety of two intravenous NAC loading regimens, i.e., 60 minutes 150 mg/k loading dose versus 15 minutes 150 mg/k loading dose. Subsequent to the assigned loading dose, all patients received 50 mg/k/4h, followed by a continuous i.v. infusion of 100 mg/k for 16 h. The protocol for this study was described in detail in my review of December 16, 2002. Briefly, this was a randomized, multi-center trial. The protocol planned for a 500 patient enrollment. Eligible were patients attended in hospitals for APAP overdose and who required NAC treatment. On April 2001, Cumberland performed an interim analysis (IA) after the enrollment of 99 patients (95 evaluable for efficacy). As described in my December 2002 review, the mean age of patients was 30 y. Efficacy was not a prospective endpoint, but a secondary assessment . The IA efficacy results showed a range of hepatotoxicity (ALT >1000 U) between 5% and 12%. No significant difference in hepatotoxicity was observed between the two loading dose regimens.

Executive Summary Section

The Division's NA letter requested Cumberland to submit data from the 212 patients who were randomized to this study up to December 30, 2002. On March 12, 2003, the study was terminated after enrollment of 223 patients Of these, 181 patients were considered evaluable. Two patients were excluded from the efficacy data: 1 patient (#024) was not formally randomized, another patient (#033) was supposed to be administered the 60 minute dose, according to randomization, but was mistakenly administered a 15 minute dose. Data of serum ALT was available on 177 patients, 108 received the 15 minute loading dose, and 69 received the 60 minute loading dose.

The efficacy results of the completed patient population were similar to the results observed in the IA. Hepatotoxicity (ALT >1000 U) was observed in six (6%) of the 108 patients who received the 15-minute loading infusion, and six (9%) of the 69 patients who received the 60-minute infusion. There was no statistical difference.

There were 56 patients who received NAC treatment within 8 h of the acetaminophen overdose. None of these patients developed serum ALT levels in the range of liver toxicity (>1000 U). In 110 (10%) patients, in whom treatment with i.v. NAC was initiated after 8 h of the overdose; 11 developed ALT levels > 1000 U/L. In an additional 10 patients, the time of NAC treatment initiation, could not be ascertained.

Reviewer Comments.

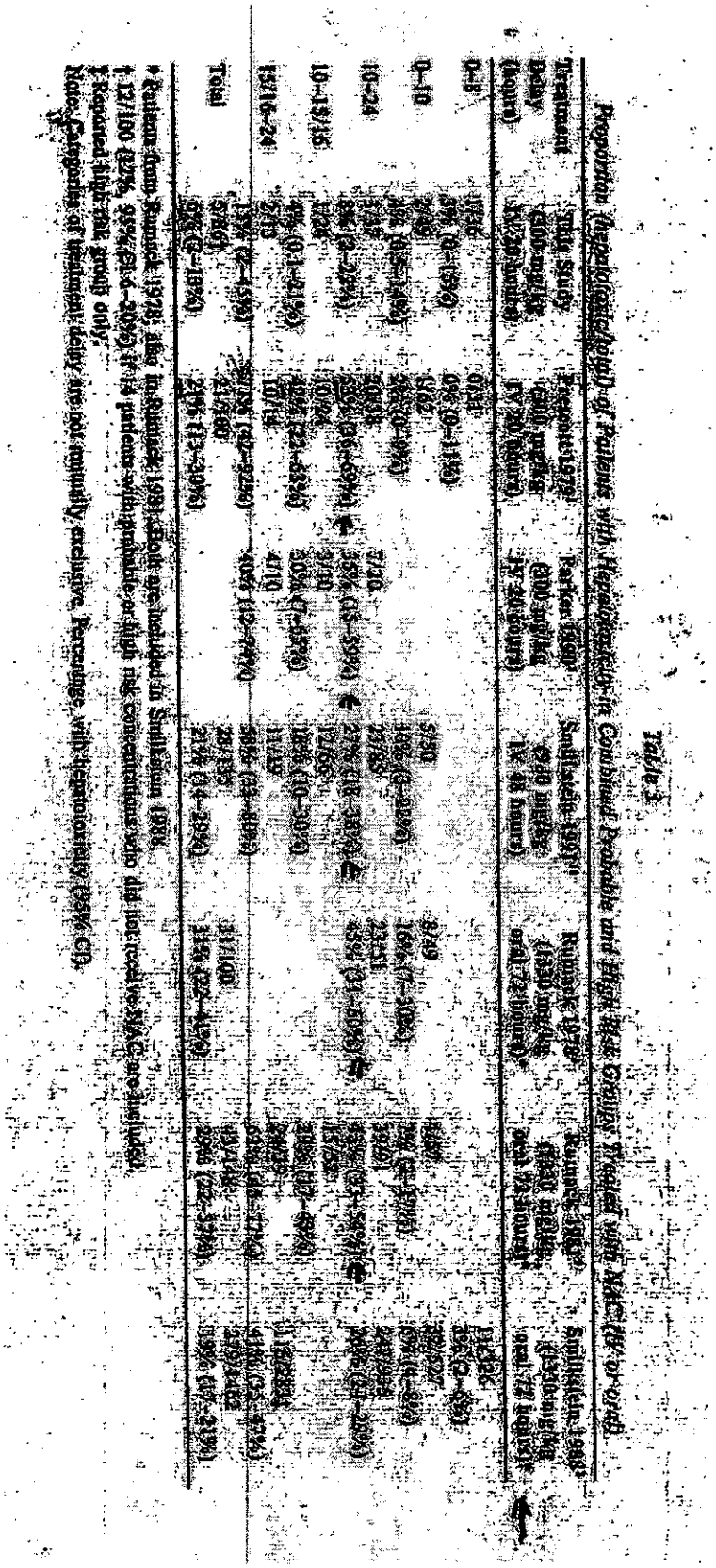
The efficacy data obtained from this safety study are of little value. As stated in my comments of the December 2002 review, the adequacy of this study is in doubt, for <40% of patients were allocated to the 60 minute loading dose, casting concerns over the randomization process, and the efficacy data were evaluated before completing enrollment, in an unscheduled IA. The redeeming data, is the corroboration that i.v. NAC is effective if given within 8 h of the APAP overdose.

Efficacy Conclusions

Based on the HATS prospective observational study conducted in Newcastle (Australia), and the large Buckley's study (*a meta-analysis*) included as part of the Cumberland's Group Database, I conclude the following:

1. Administration of intravenous NAC within 8-10 hours of an acetaminophen overdose is effective to protect against biochemical liver failure, as shown by serum ALTs below 1000 IU/L. Beyond the 10 h window, efficacy of intravenous NAC does not consistently seem to protect against liver toxicity (*as shown in next Buckley Table 3*).
2. Intravenous NAC, 300 mg/k infused over 20 h, and administered within 8-10 h of an APAP OD, is as effective as administration of oral NAC 1330 mg/kg, given over 72, (also *seen in next Buckley's Table 3*) .

Executive Summary Section



B. Review of Safety.

My first review of this NDA (*December 2002*), detailed the NAC safety profile based on the information of five submitted studies (*see the introduction section of this review*), the safety accrued by the Rocky Mountain Poison Center (*Denver, Co*), and the preliminary safety from the IA of the CM8801 NAC infusion study. As described in that first safety review, the major risk of intravenous NAC administration are anaphylactoid reactions of different degree of severity, i.e., from rash to bronchospasm, hypotension, and shock. Death in patients treated with NAC was reported in my first review, but in all of those fatal outcomes, the cause of death was either related to large overdoses of NAC, to the APAP overdose, or to other causes (suicide). In this second review of this NDA, I will supplement the described NAC safety with additional relevant information from a recent publication, namely a fatal outcome directly related to intravenous NAC, and with additional information from the database, the HATS, and completed CM8801 study.

Death.

In 2002, Appelboam et al, reported a fatal reaction to N-acetylcysteine. This case was included in the Cumberland's Case Reports Database (Page 74, Vol. 1). The following is the description of this case:

> *Appleboam VA, Dorgan PI, J Knighton. Fatal anaphylactoid reaction to N-acetylcysteine: caution in patients with asthma. Emerg Med J 19:594-595, 2002.*
>
> This 40 y woman was attended at the emergency department after taking 15 g of paracetamol (*acetaminophen*) over a 48 h period. She had a history of corticosteroid-dependent asthma and two previous admissions to ICU, once requiring mechanical ventilation. Her treatments included salbutamol nebulizers and 60 mg prednisolone/day. She also had a diagnosis of depression treated by fluoxetine, and a past APAP overdose. On arrival to the ER, she was alert, able to talk, in no respiratory distress or cyanosis. Chest auscultation was normal. She was obese (101 k). Pulse and blood pressure were normal.
>
> As antidote of the APAP overdose, she was given an initial intravenous infusion of NAC (150 mg/k over 15 minutes). After 5 minutes of infusing NAC, she complained of feeling increasingly short of breath with no other symptoms. However, chest auscultation revealed severe bilateral wheezing with poor chest expansion. The NAC infusion was stopped immediately and she was given nebulized salbutamol, 1 mg intramuscular epinephrine, 200 mg intravenous hydrocortisone, and 10 mg chlorpheniramine. Despite these measures, and an additional 1 mg intravenous adrenaline, she deteriorated, became cyanotic and went into respiratory arrest. Ventilation by bag and mask was unsuccessful, and an endotracheal tube was then inserted to assist ventilation. She subsequently suffered a hypoxic cardiac arrest from what she was brought back after nine minutes of cardiopulmonary resuscitation. In the ICU she continued to be unresponsive and with myoclonic jerks, despite adequate ventilation. Her clinical

state, brain CT scan and EEG revealed hypoxic brain injury. She died one week after admission without regaining consciousness.

Reviewer Comments

This is the first fatal outcome to i.v. NAC, due to a severe anaphylactoid reaction to an intravenous loading infusion of 150 mg/k of N-acetylcysteine, which is the loading dose proposed by Cumberland. Though the NAC loading dose was infused in 15 minutes, instead of the ——— proposed by the sponsor, there is no proof that a ——— infusion could have salvage this patient. In fact, Cumberland's study CMAX CM8801 did not reveal any significant differences in serious AEs between a 60 minutes and 15 minutes loading infusion. The significance of this case highlights the need to warn physicians about the possibility of very serious anaphylactoid reactions in patients with allergies, and the possible need to contraindicate the use of intravenous NAC in known asthma. In this patient, immediate discontinuation of the i.v. NAC, and treatment with bronchodilators and corticosteroids, did not prevent the fatal outcome.

Adverse Events in the HATS and CMAX CM8801.

The submitted databases and the HATS report included deaths, but none apparently due to NAC, but due to complications of the underlying APAP overdose, or to other causes, such as suicide.

The major recognized AE with the use of intravenous NAC is anaphylactoid reactions. The HATS reported an unusually low rate of anaphylactoid reactions. More in line with reported literature, the CMAX CM8801 had an incidence ranging from 14% to 18% of anaphylactoid reactions, with 1-2% in the sever category. The AEs from HATS and CM8801 are displayed in the next HATS Table 10.3.1 (Page 1953, Vol. 6), and CM8801 Table 10.2.2 (Page 963, Vol. 1).

Table 10.3.1
Incidence of Adverse Drug Reactions
by Number (%) of Patients

CMAX Protocol No. CM8801
Analysis of HATS Database

ADVERSE DRUG REACTION	Ingestion of APAP to NAC Treatment						TOTAL Patients First NAC Treatment		Subsequent Admission with NAC Treatment	TOTAL ADRs
	<=8 hours		>8 hours		Unknown					
	N	% of Group	N	% of Group	N	% of Group	N	% of Total	N	N
Anaphylactoid Reaction	3	1.8%	4	1.9%	0	0.0%	7	1.8%	0	7
Other Adverse Drug Reaction	13	7.8%	16	7.6%	3	13.6%	32	8.0%	4	36
Group ADR Subtotal	16	9.6%	20	9.5%	3	13.6%	39	9.8%	4	43
No Adverse Drug Reaction	151	90.4%	190	90.5%	19	86.4%	360	90.2%		
Group Total (% of Total)	167	41.9%	210	52.6%	22	5.5%	399	100%		

CMAX | Table 10.2.2 | CMAX STUDY NO. CM030

DRUG-RELATED ON-STUDY ADVERSE EVENT OCCURRENCE BY PATIENT

NUMBER (%) OF PATIENTS WITH ADVERSE EVENTS DEEMED TO BE DRUG-RELATED WITHIN THE FIRST 2 HOURS FOLLOWING DOSE ADMINISTRATION

Treatment Group	15-min				60-min			
Number of Patients	n = 109				n = 71			
Number (%) of Patients with one or more Adverse Events deemed to be drug-related within the first 2 hours following dose administration	44 (40%)				26 (37%)			
Cardiac disorders	5 (5%)				2 (3%)			
Severity:	*Unknown*	*Mild*	*Moderate*	*Severe*	*Unknown*	*Mild*	*Moderate*	*Severe*
Tachycardia NOS		4 (4%)	1 (1%)			2 (3%)		
Ear and labyrinth disorders	1 (1%)				0 (0%)			
Severity:	*Unknown*	*Mild*	*Moderate*	*Severe*	*Unknown*	*Mild*	*Moderate*	*Severe*
Ear pain			1 (1%)					
Gastrointestinal disorders	16 (15%)				7 (10%)			
Severity:	*Unknown*	*Mild*	*Moderate*	*Severe*	*Unknown*	*Mild*	*Moderate*	*Severe*
Nausea	1 (1%)		6 (6%)			1 (1%)	1 (1%)	
Vomiting NOS		2 (2%)	11 (10%)			2 (3%)	4 (6%)	
General disorders and administration site conditions	1 (1%)				1 (1%)			
Severity:	*Unknown*	*Mild*	*Moderate*	*Severe*	*Unknown*	*Mild*	*Moderate*	*Severe*
Chest tightness		1 (1%)						
Feeling hot						1 (1%)		
Immune system disorders	20 (18%)				10 (14%)			
Severity:	*Unknown*	*Mild*	*Moderate*	*Severe*	*Unknown*	*Mild*	*Moderate*	*Severe*
Anaphylactoid reaction	2 (2%)	6 (6%)	11 (10%)	1 (1%)		4 (6%)	5 (7%)	1 (1%)
Respiratory, thoracic and mediastinal disorders	2 (2%)				2 (3%)			
Severity:	*Unknown*	*Mild*	*Moderate*	*Severe*	*Unknown*	*Mild*	*Moderate*	*Severe*
Pharyngitis			1 (1%)					
Rhinorrhoea		1 (1%)						
Rhonchi						1 (1%)		
Throat tightness						1 (1%)		
Skin and subcutaneous tissue disorders	6 (6%)				5 (7%)			
Severity:	*Unknown*	*Mild*	*Moderate*	*Severe*	*Unknown*	*Mild*	*Moderate*	*Severe*
Pruritus		1 (1%)				2 (3%)		
Rash NOS		3 (3%)	2 (2%)			3 (4%)		
Vascular disorders	2 (2%)				3 (4%)			
Severity:	*Unknown*	*Mild*	*Moderate*	*Severe*	*Unknown*	*Mild*	*Moderate*	*Severe*
Flushing		1 (1%)	1 (1%)			2 (3%)	1 (1%)	

drug-related Adverse Event = AE deemed by investigator to be associated with study drug.

Reviewer Comments

The proportion of anaphylactoid reactions observed in the CM8801 study, 14% to 18%, are in agreement with the proportion of anaphylactoid reaction reported in the literature with use of intravenous NAC. Unclear are the reasons for the very low proportion of anaphylactoid reactions exhibited in the HATS data. Noteworthy, are the relatively high proportion of nausea and vomiting, i.e., 4-11% of vomiting, displayed in the CM8801 study, with use of intravenous administration of NAC. Nausea and vomiting, have been mentioned by the sponsor as the primary AEs, to justify the use of the intravenous route for NAC administration.

Safety Conclusions

The relevant findings in this supplement of intravenous NAC are the reported death of the 40 y old asthmatic woman caused by a NAC loading dose of 150 mg/k, in spite of immediate and appropriate medical intervention, and the confirmation of the already reported rate of 14 % to 18% of patients developing anaphylactoid reactions after being intravenously injected with NAC, at the dose and regimen of 300 mg/k proposed by the sponsor. Further, is the unexpected finding of up 11% vomiting in injected patients.

I therefore conclude that intravenous infusion of NAC has potential serious risks, even at the dose proposed by the sponsor, that require careful consideration when administering NAC by this parenteral route.

IV. Conclusions and Recommendations

A. Conclusions

The sponsor submitted a meta-analysis of 3079 patients treated with NAC and the HATS database from Newcastle, Australia to support efficacy of intravenous NAC. Because of the heterogeneity of the references, Cumberland's divided the meta-analysis into three databases, i.e. Case Report Database, Patient Database, and Group Database. The Case Report and Patient Database had no identifiable source of reference or lacked a comparison to oral NAC. The Group Database had seven identifiable references and was the largest database (2808 patients). The statistical methodology did not meet the standards of a combinable and integrated meta-analysis. Hence, from a statistical viewpoint, Cumberland's meta-analysis could not be used to support efficacy. Statistics notwithstanding, the Group Database revealed a markedly low incidence of hepatotoxicity as defined by serum ALT/AST <1000 IU/L in patients treated with

intravenous NAC within 8-10 hours of the APAP overdose. Two further pieces of evidence, indicates clinical efficacy of intravenous NAC. First, the 1999 Buckley et al study/meta-analysis of over 900 patients revealed similar efficacy between intravenous NAC administered at the proposed 300 mg/k, and oral NAC administered at 1300 mg/k. The intravenous NAC efficacy was largely observable when NAC treatment was given 8-10 h of the APAP overdose. Secondly, the Hunter database, which compared the intravenous NAC, 300 mg/k to no treatment, confirmed the efficacy of the i.v. NAC when administered within the 8-10 h post-overdose period. In this Hunter database, a small number of overdosed patients treated within the 8-10 h early period with gastric lavage and/or charcoal alone, exhibited similar low incidence of hepatotoxicity.

The safety profile of the intravenous NAC was supplemented in this second submission with a fatal outcome reported in the literature of 2002. The patient, an asthmatic, developed irreversible bronchospasm and respiratory failure shortly after a loading infusion of 150 mg/k of intravenous NAC administered as the antidote of an APAP overdose. The present submission further corroborated that a proportion close to 1 out of 5 patients given intravenous NAC develop anaphylactoid reaction, mostly mild or moderate in severity.

Based on the presented data, I conclude that there is evidence demonstrating that intravenous NAC, administered within 8-10 h from an APAP overdose, is effective in preventing hepatotoxicity defined by liver transaminases higher than 1000 IU/L. I also conclude that there are serious risks of intravenous NAC use in patients with asthma and allergies to warrant a warning to physicians, but overall, the benefits of intravenous NAC administration outweighs the risks.

B. Recommendations

I recommend the following:

1. Approval of Cumberland's intravenous formulation of N-acetylcysteine (ACETADOTE®), for the prevention of hepatotoxicity in patients overdosed with acetaminophen.

2. The INDICATION section of the label should inform that intravenous infusion of N-acetylcysteine has been shown to be effective within an 8-10 hour period of the acetaminophen overdose. No effectiveness has been shown if administered after 10 hours from the overdose.

3. The label should include a WARNING section stating that serious anaphylactoid reactions, including death, have been reported in patients with asthma administered with an intravenous N-acetylcysteine dose.

4. Administration of ACETADOTE® should be contraindicated in individuals with a history or diagnosis of asthma, even if medicated with bronchodilators or corticosteroids.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Prizont
12/30/03 12:47:02 PM
MEDICAL OFFICER

Hugo Gallo Torres
1/5/04 02:28:06 PM
MEDICAL OFFICER
The GI Medical Team Leader agrees with Dr. R. Prizont's recommendatiion for regulatory action. NDA 21-539/NOOO/BZ, ACETAD for the prevention of acetaminophen overdose-induced hepatoxicity, should be approved.

Center for Drug Evaluation and Research

Division of Gastrointestinal and Coagulation Drug Products

Clinical Review Cover Sheet

NDA: 21-539

Sponsor: Cumberland Pharmaceuticals Inc.

Drug: Acetadote® (Acetylcysteine injection)

Date the Document was Received by CDER: July 1, 2002

Date the Document was Received by the DGICDP (HFD-180): July 3, 2002

Date the Document was Received by the Medical Officer: July 18, 2002

Filing Date: August 30, 2002

Date of Draft:: December 16, 2002

PDUFA Due Date: January 3, 2003

Medical Officer: Robert Prizont, MD

Table of Contents

Clinical Review for NDA 21-539

Executive Summary

I. Recommendations

A. Recommendation on Approvability

My recommendation is not to approve the proposed use of intravenous formulation of N-acetylcysteine for acetaminophen overdose treatment. The sponsor proposes a 21 hours of intravenous N-acetylcysteine dosing regimen (*described below in the section of "dosing"*) *"for the treatment* [redacted]. [redacted] My recommendation is based on the lack of adequate and well-controlled clinical trials to show substantial evidence of effectiveness of the proposed intravenous N-acetylcysteine dosing regimen for the appropriate indication, i.e., *an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.* (taken from the approved oral N-acetylcysteine label)

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No proposed recommendations at this time.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The sponsor submitted data on intravenous (i.v.) N-acetylcysteine obtained from five historical publications, reported in US and UK medical journals. A prospective protocol of two of these studies conducted in the US under identical design, was the only submitted prospective documentation. The interim analysis (IA) from an ongoing clinical trial, conducted on 20% of the prospectively planned patient population, was the other documentation provided. The data of the five historical reports and the IA were designated by the sponsor as "Primary Studies". The design of these Primary Studies was open-label; two were randomized, and one was placebo-controlled. They included a total of 396 patients treated with various intravenous dosing regimens of N-acetylcysteine.

B. Efficacy

N-acetylcysteine was introduced over 20 y ago as antidote to prevent liver failure and high mortality related to acetaminophen overdose (OD). Mortality rates cited in early publications on acetaminophen overdose (1970's and 1980's) were >30%. In 1984, an oral formulation of N-acetylcysteine (NAC) was approved in this country as an antidote for acetaminophen OD. The approved treatment included initial gastric lavage, oral administration of activated charcoal, followed by 1330 mg/kg oral NAC given over 72 hours. In 1999, Buckley et al, published a comprehensive meta-analysis of oral and intravenous administration of NAC (*Buckley NA et al. Oral or intravenous N-acetylcysteine: Which is the treatment of choice for acetaminophen (Paracetamol) poisoning? Clinical Toxicology, 37:759-767, 1999*). It integrated 981 patients gathered from MEDLINE, EMBASE, the Cochrane collaboration trial register, cross referencing from the authors results and other series, review articles, and consultation with experts. Included in the analysis were studies with enrollment of at least 20 patients. As shown in the authors Table 2, the results revealed unexpected low mortality linked to acetaminophen overdose, 0.2 %, with a similar low 3% morbidity (*represented by biochemical evidence of liver failure, i.e., serum ALT >1000 IU*). Low mortality and morbidity rates were observed in patients who were untreated, treated with NAC, or with other drugs. Only 21% of patients included in the meta-analysis had received NAC.treatment.

Table 2

Comparison of Patients With and Without Hepatotoxicity

	Hepatotoxicity (n=30)	Others (n = 951)	p value
Median age (range)	24 (14–70)	24 (0–89)	0.85
Male	12 (40%)	342 (36%)	0.65
Median time to presentation, min (range)	1238 (30–5160)	165 (5–6540)	0.0001
Median amount of acetaminophen ingested, mg (range)	24,000 (5,000–50,000)	10,000 (120–77,000)	0.0001
Late presentation (>24 h)	12 (40%)	28 (3%)	<0.0001
Probable or high risk concentration (<24 h)	12 (40%)	88 (9%)	<0.0001
Received NAC	14 (47%)	191 (20%)	0.0004
Median time to NAC, min (range)	923 (330–2760)	525 (20–2970)	0.0007
Length of stay, hours (range)	73 (10–285)	17 (0.9–2685)	0.0001

Data shown as n (%) or median (range). p value using Wilcoxon Rank sum test or Yates' continuity corrected chi-square test.

The morbidity and mortality of acetaminophen OD in this rather recent meta-analysis serves as introduction to assess the efficacy and safety data provided by the sponsor. The order of the next brief summary of efficacy data from the Primary Studies, is the order submitted by the sponsor in its table of Primary Studies (*see Section B, Clinical Review Section*).

1. R Keays et al (*BMJ, 303:1026-1029, 1991*). Randomized, placebo-controlled, open-label trial. NAC was given intravenously for 20 h and 15 min (150 mg/k loading dose given in 15 min, 50 mg/k for 4 h, and

continuous infusion of 100 mg for 16 h). All 50 patients, 25 given placebo and 25 treated with i.v. NAC had hepatic failure (ALT >1000 IU) at entry. Typically, mortality rate in acetaminophen OD is used as an efficacy index of NAC therapy. This study reported a mortality rate in the NAC treated patients of 52%. Though this rate was lower than the mortality in placebo patients (80%), it constitutes a very high mortality rate when compared to all reports on NAC therapy in acetaminophen OD.. The authors reported benefits with NAC therapy in the proportion of patients with cerebral edema, renal failure, hypotension, level of encephalopathy. The aim of this study was to assess any benefit of i.v. NAC in bona fide liver failure. It was not designed to determine efficacy of i.v. NAC as antidote to prevent liver failure in acetaminophen OD, which is the purpose of this NDA..

2. HE Perry et al. (*J Pediatr 132:149-152, 1998*).. Non-randomized, open-label study. The authors treated 25 adolescents (mean 15.5 y of age) with i.v NAC, i.e., 140 mg/k loading dose, 70 mg q4 h for a total therapy period of 52 h. This 25 adolescents were compared with a historical control of 29 patients treated for 72 h with oral NAC. Seven percent in the oral and 8% in the i.v. group developed severe hepatotoxicity. Prothrombin time was significantly prolonged in the i.v.. NAC group. This is an uncontrolled study of a pediatric population, with no statistical analysis.

3. MJ Smilkstein et al (*Ann Emerg Med 20:1058-1063, 1991*). Identical study design as the previous Perry study and shorter period of intermittent i.v. NAC dosing regimen (48 h). The authors evaluated liver biochemical abnormalities (ALT, AST, serum bilirubin) in one hundred twenty three patients (mean 21 y, 79% women) treated with i,v, NAC after various post-acetaminophen OD intervals (<10 h or > 10 h). Patients treated <10 h after acetaminophen OD had significantly lower serum ALTs values than patients treated between 10-24 h after the OD. The authors compared the results to historical data. There were 5 deaths in all-entered patients (1 suicide, 4 died of liver failure). Seven i.v. NAC treated patients were excluded from the analysis. As with the previous Perry study, there was no parallel control treatment..

4. T.E. Oh. (*Med J Aust 1:664-665, 1980*). This is a one page report of an open-label NAC treatment. Eleven patients (10 females) with acetaminophen OD were treated for 13 h with an i.v. NAC dosing regimen (150 mg/k loading dose, followed by 4 h of 50 mg/k, and 8 h continuous infusion of 100 mg/k). Ten patients recovered without complications. One patient had liver failure (serum ALT >1000 IU). No conclusions can be drawn from this report in only 11 patients without concomitant parallel or historical control,

5. LF Prescott (*Ann Intern Med 141:386-389, 1981*). Historical active-active comparison, open-label. The i.v. NAC dosing included a 150 mg/k 15 min loading dose, followed by 4 h 50 mg/k, and 100 mg/k given in two 8 h periods. The aim of this study was to show that the interval of 10 h after the acetaminophen OD is important. The mean serum ALT was 3814 IU in i.v. NAC patients treated between 10-24 h post-overdose; greater than the mean ALT of 2022 IU observed in the supportive control group. Similar to the previous two studies, there was only historical comparison of data with no parallel control treatment and no statistical analysis.

6. Interim Analysis of CM8801. The sponsor did an interim analysis of 20% of a planned 500 patient enrollment. The study was designed to compare two periods of administration of a 150 mg/k i.v. NAC loading dose, i.e., 15 min versus a 60 minute. Each loading dose was followed by a 4 h 50 mg/k i.v. infusion and a 16 h i.v. continuous infusion (total 21 h NAC treatment). The IA revealed 35 patients in the 60 min group and 61 in the 15 min group. Only a total of 29 patients (11 in the 60 min group) were enrolled within 8 h post-acetaminophen OD (the interval where NAC therapy appears to be more effective). The comparison of liver enzymes in the serum of the 29 patients treated within 8 h post OD showed no differences in efficacy between the groups. The sponsor noted that no efficacy conclusions could be drawn from such small number of patients.

Conclusion on Efficacy. Only three of the five historical reports (Primary Studies 2,3,5) enrolled more than 20 patients and were aimed to show evidence of i.v. NAC efficacy as preventive antidote in acetaminophen OD. All were open-labeled and lacked a parallel control treatment comparison. The three studies revealed variable NAC efficacy. None of the studies used the intravenous dosing regimen proposed in the label. Hence, the data from these uncontrolled studies cannot be used to comply with the regulatory requirement of substantial efficacy obtained in adequate and well-controlled trials.

C. Safety

The Primary Studies submitted by the sponsor listed a total of 22 deaths in patients treated the i.v. NAC versus 24 deaths in patients treated with "other" treatments (oral, cysteine, methionine, supportive treatments). In another safety compilation , anaphylactoid reactions, including bronchospasm (6%), angioedema (8%), rash, pruritus, vasodilation (10%), urticaria (6%), nausea (10%), anapylactic shock (2 cases), death (3 cases), were the serious AEs, extracted from a total of 427 AEs which occurred in 254 patients (out of 1050 NAC treated patients).provided to the sponsor by the Rocky Mountain Poison Center of Denver (CO).

Conclusion on NAC Safety. The overall safety range appears acceptable. However, the provided data-base reveals that administration of i.v. NAC may induce serious anaphylactoid reactions in susceptible individuals.

D. Dosing

The label proposes a ⎓ h I.v. NAC dosing regimen encompassing the following periods:

Loading Dose. 150 mg/kg in 200 ml of 5% dextrose, infuse intravenously for ———————

Maintenance Dose. 50 mg/kg in 500 ml of 5% dextrose, infuse intravenously over 4 hours followed by 100 mg/kg in 1000 ml 5% of dextrose, infuse intravenously over 16 hours.

E. Special Populations

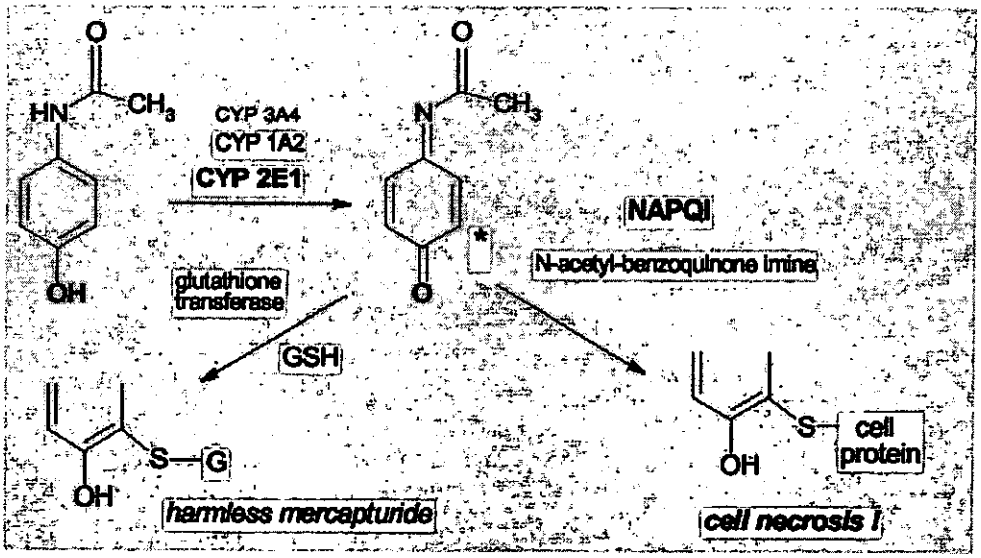
The pediatric efficacy in ages < 10 years was inadequate (3 patients). The aforementioned study by Perry (Primary Study 2) was conducted in 25 adolescents (mean 15.5 y). An historical review revealed 15 deaths associated with use of i.v. NAC in 104 pediatric patients. One case was due to excessive i.v. NAC dose. Twenty minutes after the NAC infusion, this child became cyanotic and never recovered from a circulatory collapse. One death occurred in a 15 y old female treated with i.v. NAC for acetaminophen OD. The15 pediatric deaths included fatal outcomes in 10 premature infants. One infant died three hours after birth; the mother had been treated with i.v. NAC for acetaminophen OD. Ten other premature infants had associated serious concomitant diseases. There were 2 pediatric reports of seizures following i.v. NAC infusions. Other serious AEs reported in pediatric populations are similar to those described in adults, with anaphylactoid reactions being the most frequents AE. The sponsor did not provide data on any other special populations

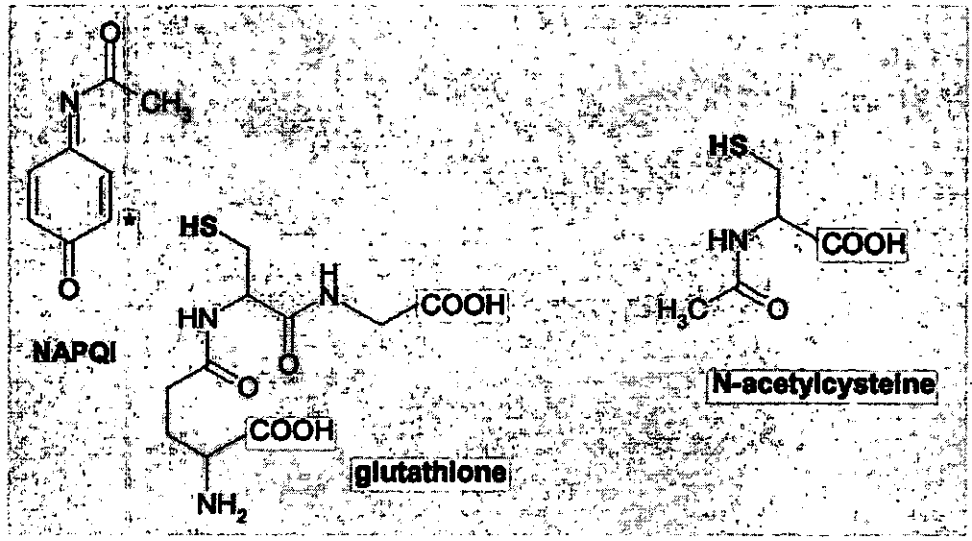
Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

An oral formulation of N-acetyl-L-cysteine (NAC) is approved for use for the treatment of actaminophen overdose [acetyl-para-aminophenol (APAP overdose)]. NAC is the nonproprietary name of the N-acetyl derivative of the naturally occurring aminoacid L-cysteine. The sponsor proposes the name of ACETADOTE® as trade name for its intravenous formulation of NAC. NAC belongs to the class of drugs known as reduced sulphydryl agents. As reduced agents, this class of drugs prevent cell oxidation and cell death, by acting as cytoprotective H^+ donors. In the liver, NAC behaves as a glutathione substitute. The following figures, taken from the presentation by Dr. John Senior, at the Advisory Committee on Acetaminophen Toxicity (September 19, 2002), illustrates the normal metabolic activation of acetaminophen, the formation of the harmful metabolite NAPQI, and detoxification by glutathione or NAC.





The following are the proposed Indication, Dose, Regimens, and Age Groups.

Indication. .ACETADOTE® is "*indicated for i.v. treatment*

Dose and Regimens. The sponsor's proposed label recommends a time of administration in suspected APAP overdose, a *loading* dose, and a *maintenance* dose. They are (*verbatim*), the following:

Loading Dose. 150 mg/kg in 200 ml of 5% dextrose, infuse intravenously for

Maintenance Dose. 50 mg/kg in 500 ml of 5% dextrose, infuse intravenously over 4 hours followed by 100 mg/kg in 1000 ml 5% of dextrose, infuse intravenously over 16 hours.

Age Groups. The proposed label does not specify age groups. The Primary Studies studies were conducted in adults (≥18 years) and adolescents (15.5 y). The label state the following regarding NAC use in the elderly,

A pharmacokinetic (PK) study in healthy newborns is the information on safety included for "*Pediatric Patients*" in the *Indication* section of the proposed label. This label section states that "*no adverse effects were noted during iv infusion with acetylcysteine at a mean rate of 8.4 mg/kg/h for 24 hours to 10 preterm newborns ranging in gestational age from 25 to 31 weeks and in weight from 500 to 1380 grams in one study (Study 1) or in 6 newborns ranging in gestational age from 26 to 30 weeks and in weight from 520 to 1335 grams infused with acetylcysteine at. 0.1 to 1.3 mg/kg/h for 6 days (Study 2). .Elimination of acetylcysteine was slower in these infants than in adults; mean elimination half-life was 11 hours (Study 1)*".

i. Reviewer Comments

B. State of Armamentarium for Indication(s)

In the US, the oral NAC solution (Mucomyst® and Generic oral NAC formulations) is the only current approved formulation. The approved label indication for the oral NAC solution, reads as follows (*reproduced from the Mucomyst® label*):

- *Acetylcysteine, administered orally, is indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. It is essential to initiate as soon as possible after the overdose and, in any case, within 24 hours of acetaminophen ingestion.*

The following is the list of approved and marketed oral and inhalant NAC preparations, as provided by the sponsor on Page 3, Vol. 1.11.

Table 1 **Approved NDA Applications for NAC**

Application Number[a]	Dosage Form	Strength	Active Ingredient	Company
73-664	Solution; Inhalation, Oral	10%	n-acetylcysteine	Abbott
74-037	Solution; Inhalation, Oral	20%	n-acetylcysteine	Abbott
13-601	Solution; Inhalation, Oral	10%	n-acetylcysteine	Apothecon
13-601	Solution; Inhalation, Oral	20%	n-acetylcysteine	Apothecon
72-323	Solution; Inhalation, Oral	10%	n-acetylcysteine	Bedford
72-324	Solution; Inhalation, Oral	20%	n-acetylcysteine	Bedford
70-575	Solution; Inhalation, Oral	10%	n-acetylcysteine	Dey
70-576	Solution; Inhalation, Oral	20%	n-acetylcysteine	Dey
71-364	Solution; Inhalation, Oral	10%	n-acetylcysteine	Faulding
71-365	Solution; Inhalation, Oral	20%	n-acetylcysteine	Faulding
72-489	Solution; Inhalation, Oral	10%	n-acetylcysteine	Luitpold
72-547	Solution; Inhalation, Oral	20%	n-acetylcysteine	Luitpold
72-621	Solution; Inhalation, Oral	10%	n-acetylcysteine	Roxane
72-622	Solution; Inhalation, Oral	20%	n-acetylcysteine	Roxane

[a] Source of information in Table Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations Current through December 2001.

Clinical studies have included methionine and cysteine as active i.v. treatment comparators, but these compounds never gained preference as alternative to the use of i.v. NAC.

C. Important Milestones in Product Development

There was a single meeting between Cumberland Pharmaceuticals (the sponsor of this NDA) and the HFD-180 Division. It took place on December 15, 2000. The sponsor's objectives were to obtain the following information: (a) input on the proposed 505(b)(2) application, (b) input related to the proposed labeling, (c) input on the existing non-clinical and clinical data on the i.v. formulation, (d) input on the existing available literature and existing published data on "an approved product in the US". The relevant responses from the Division were the following:

- Specify which will be the pivotal studies and which will be supportive studies. Regarding documentation from available or published data of pivotal studies, the Division recommended "*attempting to obtain as much source documentation for the pivotal studies as possible. The documentation should include protocols, the informed consent form, case report tabulations, and case report forms deaths and dropouts. A decision regarding the filability of your application will be made upon its submission and based on a filing review of the NDA as submitted*". The Division added that it may be useful to obtain data and study reports that provided the basis for the approval of intravenous N-acetylcysteine

in foreign countries (i.e.., Europe and/or Canada). The Division noted that *since full study reports are still required, the requirements for source data for a 505(b)(2) applications are almost as strict as those for a 505(b)(1) application.* Source documents are necessary to verify authenticity of literature reports, assessment of protocol, design for adequacy, and IRB approvals. Retrospective, uncontrolled, or open-label studies, do not provide the strong, unequivocal evidence necessary for pivotal studies. The firm stated that they will attempt to obtain the best source data possible and would submit the results of their search for our review and comments. The Division added that safety and pharmacokinetic (PK) data may be obtained from patients treated with i.v. NAC indications other than APAP toxicity. The Division explained that if the firm is relying on safety and effectiveness for its i.v. formulation, from the approved oral NAC, they must perform a bridging bioavailability study.

Cumberland did not request additional meetings since the described meeting of December 15th, 2000

- On October 19, 2001, the Office of Orphan Drug Products granted a designation request for NAC i.v. NAC.

- NDA 21-539 was received by this Agency on July 1, 2002. It was submitted as a 505(b)(2) application and received priority status. During the Filing Pre-Meeting, on August 30, 2002, there were concerns about the appropriateness for filing this application. The concerns were based on the lack of available documentation on any of historical literature, including those classified by the sponsor as "Primary Studies". This medical officer (MO), with concurrence from the Medical Team Leader recommended not to file NDA 21-539 (*review placed on DFS on August 23, 2002*). This recommendation was based on the absence for "proof" of safety, efficacy, and adequacy of the historical Primary Studies, i.e., patient consent form signed in accordance to the Helsinki Agreement, prospective protocols, prospective randomization, list of patient tabulation, list and reasons for discontinuations, Case Report Forms of patients discontinued due to adverse events. The Acting Division Director, Dr. Victor Raczkowski, made the decision to file the NDA. A letter was sent to Cumberland Pharmaceutical informing it of the decision to file the application and requesting further information. The requested clinical information was the following (*scanned*):

Clinical

1. **Provide a tabular summary of clinical efficacy data (and text if available) including; dates of randomization; discontinuations; dates of efficacy endpoint measurements; data on subsets of patients according to gender, sex, race, and age; and patient narratives in WORD 97.**
2. **Provide prospective protocols of placebo-controlled trials or other relevant pivotal trials.**
3. **Provide patient informed consent forms or forms signed by investigators or institutional IRBs certifying that patients were enrolled according to the latest amended Declaration of Helsinki.**
4. **Provide an assessment of the safety and effectiveness of ACETADOTE® in pediatric patients as required under 21 CFR 314.55.**
5. **Provide a revised Form FDA 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators" including a list of relevant clinical investigators as required under item #2.**
6. **Provide a copy of the proposed unannotated labeling on diskette in WORD 97.**

Other Relevant Information

Intravenous NAC formulations are approved and marketed in many countries of Europe and in Canada. The formulation proposed by Cumberland is similar to the NAC i.v. formulation marketed in Australia, New Zealand and Canada. Although there is no i.v. NAC formulation approved in this country, some medical care institutions have used filter-sterilized 20% NAC oral solutions as i.v. formulations to treat APAP overdose in patients who are unable to be treated by the oral route. In the December 2000 meeting with the Agency, the sponsor reported that during the 1994-1998 period, 50,552 US patients were treated with NAC for APAP overdose; 2,517 were given NAC by the intravenous route. According to the sponsor, this information of i.v. use in the USA is based on data provided by the American Association of Poison Control Centers and the Rocky Mountain Poison and Drug Center.(Denver, CO).

Oral NAC solution (Mucomyst®, Mead Johnson, co-sponsored by McNeil Lab.) for APAP overdose, was approved on October 1984, under NDA 13-601. The approval was based on the report of a pivotal large single-center multi-clinic, open-label trial conducted under a prospective protocol titled *Management of APAP Overdose with a NAC Oral Preparation*. The trial was conducted by the University of Colorado Medical Center, Denver, CO. Barry Rumack, MD was the coordinator. A prospective protocol for this study was submitted by Mead-Johnson in IND 442. McNeil also co-sponsored the study in IND ——— NDA 13-601 included as supportive trials publications by Prescott et al, on i.v. NAC administration in APAP overdose. The primary study by Rumack, conducted between 1976 and

1978, which served as basis for approval of NDA 13-601, enrolled 662 non-selected patients with potentially hazardous APAP doses; 598 patents were treated with NAC. Seventy seven control patients received supportive treatment. The results revealed 6 deaths in the 77 controls versus 0 in the 598 NAC patients.

E. Important Issues with Pharmacologically Related Agents

Methionine and cysteine are chemical compounds with similar pharmacological anti-oxidant activity as NAC. Methionine is approved by the British Pharmacopeia as alternative oral antidote to treat APAP overdose (OD). Cysteine has been used off-label for the treatment of cystinosis, Currently, there are studies to develop systemize eye drops as treatment for deposits of cystine crystals in the cornea.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

- Four major issues related to chemistry: (a) the manufacturing source does not comply to the USP specifications, (b) drug product specifications are not satisfactory, (c) incomplete information provided for the drug product stability, (d) the container closure system is inadequate. The Division of Biometrics (Dr. Tom Permutt) has evaluated the randomization deficiencies revealed by the uneven proportion of the two patient groups described in the CM8801 IA. He has concluded that the CM8801 trial was not design to provide evidence of efficacy, and the results of the IA, confirm the lack of efficacy. It further offers comments on the lack of strong evidence of efficacy revealed by the submitted Primary Studies.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The reviewer for biopharmaceutics (Dr. Albert Chen) summarized the PK findings in the following sentence:

- Fourteen literature articles were submitted to support the PK of i.v. NAC in healthy volunteers and APAP OD patients. The i.v. NAC dosing regimen included in the submitted data was similar, but not identical, to the proposed i.v. NAC dosing regimen. Lacking was information on the 150 mg/k loading dose administered over _____ (as proposed by the label). The reviewer attempted to obtain a PK profile of the proposed i.v.

NAC dosing regiment in a simulated comparison with the approved oral NAC This computerized simulated link was unsuccessful.

B. Pharmacodynamics

No pharmacodynamic data were provided by the sponsor.

IV. Description of Clinical Data and Sources

A. Overall Data

The sponsor included 6 trials as "*Primary Studies of Acetaminophen Overdose, Other Studies APAP Overdose and Other Published Uses of NAC*" [Vol 9 (1.9)]. Among the Primary Trials, the Interim Analysis of CMAX Study No CM8801, was the only prospective data on the i.v. NAC dose regimen. The other 5 studies were historical published reports. The submission included prior publications of open label studies on NAC and APAP OD (94 subjects), retrospective studies (1493 subjects), and case reports (20 subjects).

B. Tables Listing the Clinical Trials

Tabular Summary of Clinical Efficacy Data, Primary Studies

Reference	Study Design, No. of Sites	Route*, NAC Dose Regimen, Trade Name, Manufacturer	Study Population	NAC:Control Male/Female Age (years):Mean (Range)	Efficacy Parameters Evaluated	Efficacy Results
Keays (1991)	Randomized, Placebo controlled Single Site	iv LD: 150 mg/kg over 15 minutes MD: 50mg/kg over 4 hours followed by 100 mg/kg over 16 hours Trade name NK	Fulminant hepatic failure	25:25 21M/29F Age: 34(16 to 60)	Laboratory testing including PT	Survival was significantly greater (p=0.037) in the NAC group compared to the placebo-treated group (12 of 25 [48%] and 6 of 25 [20%], respectively). A lower incidence of cerebral edema and cardiovascular dysfunction was also observed in the NAC-treated group compared to the control group.
Perry (1998)	Open label, iv vs. oral Multi Site	iv, po LD: 140 mg/kg over 60 minutes MD: 12 doses of 70 mg/kg every 4 hours Sterile, pyrogen free NAC solution, Bristol-Meyers	Pediatric patients with APAP overdose	25 iv: 29 po 6M/48F Age: 15.6 (±3.3)	Laboratory testing, including AST, ALT, bilirubin, and PT	A 52-hour iv NAC infusion was as effective as a 72-hour oral NAC dosing regimen in the treatment of APAP overdose.
Smilkstein (1991)	Open label Stratification based on APAP concentrations Multi Site	iv LD: 140 mg/kg iv over 60 minutes MD: 12 doses of 70 mg/kg iv every 4 hours Sterile, pyrogen free 20% NAC, Bristol-Meyers	Young adults and children presenting with APAP overdose	179*:0 M/F NK, but mostly F Age: 21(9.6)	Laboratory testing, including ALT and AST	A 48-hour iv NAC treatment was considered as efficacious as other NAC regimens when started within 10 hours of APAP overdose.

Reference	Study Design, No. of Sites	Route[a], NAC Dose Regimen, Trade Name, Manufacturer	Study Population	NAC:Control Male/Female Age (years):Mean (Range)	Efficacy Parameters Evaluated	Efficacy Results
Ott (1980)	Open label Historical control Single site	iv LD: 150 mg/kg over 15 minutes MD: 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours Mucomyst, Mead Johnson	APAP overdose	11:0 10M/1F Age: 33 (15 to 61)	Laboratory testing, including AST, bilirubin and PT	All patients recovered.
Prescott (1981)	Open label Positive controlled Single site	iv LD: 150 mg/kg over 15 minutes MD: 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours Mucomyst, Mead Johnson	Adults with APAP overdose	100 NAC: 87 supportive therapy only (historical): 60 cysteamine or methionine (historical) M/F NK Age: 33 (13 to 82) (NAC patients only)	Frequency of liver damage and laboratory testing	iv administered NAC was considered the safest and most effective treatment for APAP poisoning, especially if administered within 10 hours of APAP ingestion.
CMAX Study No. CM8901	Randomized prospective Loading dose comparison Multicenter	iv LD: 150 mg/kg over 60 minutes or 150 mg/kg over 15 minutes MD: 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours Trade name and manufacturer not recorded.	APAP overdose	98:0 (61 patients randomized to the 15-minute treatment arm and 35 patients randomized to the 60-minute treatment arm) 26M/70F Age: Male: 33 (17 to 60) Female: 30 (15 to 53)	Laboratory testing, including routine clinical chemistry, liver function tests, APAP concentrations, and coagulation tests	Observed rates of hepatotoxicity for the 2 dose regimens were 5% (3 patients out of 61) for the 15-minute loading dose regimen and 12% (4 patients out of 34) for the 60-minute regimen. With the relatively small number of patients involved in this analysis, the difference between the hepatotoxicity rate in the 2 groups is not statistically significant.

[a] iv: intravenous; LD: loading dose; MD: maintenance dose; NK: not known; po: per os (oral)
[b] A total of 223 patients enrolled; 179 patients met all the inclusion criteria and were reported in the reference

C. Postmarketing Experience

There were no post-marketing data provided by the sponsor.

D. Literature Review

This NDA is largely based on historical publications. The literature included in the Primary Studies and the meta-analysis included by this reviewer in the Executive Summary of Effectiveness suffice as background literature on the subject of i.v. NAC and APAP OD.

V. Clinical Review Methods

A. How the Review was Conducted

The following steps were followed:

1. Review of the proposed Indication and Dosing Regimen.

2. Review of prospective documentation, e.g., protocols, IRBs, CRF.
3. Review of the Primary Studies to assess efficacy and safety.
4. Review of literature (if needed).
5. Conclusion on efficacy based substantial evidence of effectiveness.
6. Based on steps 2,3,4,5, issue of recommendations for regulatory actions.

B. Overview of Materials Consulted in Review

The material consulted were Vol. 2, 9, 10, 11, and amendments submitted by the sponsor on October 28, Nov 4, Nov 15, Nov 27, December 3, 2002.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The methodology to assess quality and integrity was a combination of the elements included in subsection A (*How the Review was Conducted*) and the elements included in the immediate subsection D .

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The enrollment of patients according to the Helsinki Agreement is known for Primary Studies 2 (Perry et al), 3 (Smilkstein et al), and Study CM8801. There was no documentation on this subject for Primary Studies 1 (Keays et al), 4 (Oh) and 5 (Prescott).

E. Evaluation of Financial Disclosure

The sponsor provided no evidence of financial conflict of interest with investigators enlisted in CM8801 (Item 5, Page 151, Vol. 1, October 28, 2002 submission).

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The conclusion on efficacy of the proposed intravenous dosing regimen will be based on the presented Primary Studies submitted by the sponsor. Specifically, the questions that need to be addressed in the submitted primary studies are the following: Are the presented data showing substantial efficacy to support the appropriate indication (prevention of liver failure)? Are the results of the submitted primary studies based on the intravenous dosing regimen proposed in the label? As will be explain in

my comments of each study and conclusion, the submitted Primary Studies fell short of proven substantiate evidence of effectiveness and applicability of the dosing regimen.

B. General Approach to Review of the Efficacy of the Drug

This reviewer's approach to determine efficacy was based on the review of results from the six sources listed in Section B of this Clinical Review (Tables Listing the Clinical Trials), designated by the sponsor as *Tabular Summary of Clinical Efficacy Data, Primary Studies*. The results in each one of the submitted "Primary Studies" were examined by the following:

(a) Prospective design aimed to adequately test i.v. NAC as preventive drug therapy against the development of hepatic failure after an APAP OD. The prospective study design was examined for the inclusion of procedures that may minimize bias, i.e., randomization, blinding, placebo or active control treatment groups

(b) NAC i.v. dose regimen that matches the sponsor's proposed i.v. dose regimen included in the proposed label.

(c) Statistical significance of efficacy of the tested i.v. NAC, administered at the proposed doses and regimen over a placebo or active control (two-tailed $p \geq 0.05$) in the prevention of hepatotoxicity in APAP OD.

(d) Reproducible evidence of i.v. NAC efficacy for the appropriate indication (prevention of liver failure in APAP OD) at the proposed doses and regimen of administration.

C. Detailed Review of Trials by Indication

As stated, five of the six primary studies are published reports. According to the information provided, the submission includes the 1983 prospective protocol of two historical studies (Page 0007, Vol. 1., 21-539/N-000-BZ). The Primary Studies will be described in the order placed by the sponsor in its *Tabular Summary of Clinical Efficacy Data. Primary Studies (see Section B, this review).*

- **R. Keays et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 303:1926-1029, 1991,**

Objective: "To see whether i.v. acetylcysteine would improve outcome in patients with fulminant hepatic failure after paracetamol overdose".

Design: Randomized, placebo-control, open-label. The authors stated in the report that *acetylcysteine could not be blinded because the solution has an easily identifiable pungent aroma.*

Center. UK, single-center (The Institute of Liver Studies, King's College Hospital, London).

Intravenous NAC Dose-Regimen. Loading dose of 150 mg/kg given in 15 minutes, followed by a 50 mg/kg over 4 h, followed by a continuous infusion of 100 mg/kg over 16 hours (1 liter).

Brief Summary of Patients and Results. Patients with fulminant hepatic failure after APAP OD were eligible for the trial. Fifty patients, admitted to the "liver failure unit", were enrolled in the study; 25 patients randomized to i.v. NAC, and 25 to i.v. placebo. All patients had a pulmonary artery line to assess fluid wedge filling pressure and a radial arterial line. Oliguric patients with a wedge pressure of >12 mm Hg were given dopamine infusion and/or hemodialysis. Patients with grade 4 encephalopathy were "electively ventilated". Based on the admission arterial pH levels (<7.3), prothrombin time (>100s), serum creatinine concentration (>300 μmol/l), and grade of CNS confusion, patients were classified as fulfilling at least one criterion for "poor prognosis". The following Table 1 (*scanned*) lists the demographics.

TABLE 1—*Characteristics of study groups. Except where stated otherwise values are medians (ranges)*

	Acetylcysteine	Control
No of patients	25	25
Age (years)	33 (17-60)	34 (16-58)
Sex (M/F)	12/13	9/16
Hours from overdose to presentation to referring hospital	28 (16-36)	32 (16-48)
Hours from overdose to admission to liver failure unit	53 (36-80)	56 (38-96)
Values at entry to trial:		
Serum creatinine (μmol/l)	246 (86 to 620)	247 (71-574)
Arterial pH	7·39 (6·89 to 7·48)	7·39 (7·08-7·53)
Prothrombin time (s; control time 15 s)	115 (29 to 180)	140 (29 to 180)
No of patients fulfilling criteria for poor prognosis:		
Admission pH <7·30	8	5
Prothrombin time >100 s+serum creatinine >300 μmol/l+grade 3 or 4 coma	9	11
Rise in prothrombin time on day 4 compared with day 3 after overdose	5	5
No of patients fulfilling at least one criterion for poor prognosis	17	18

The authors report that 48% (12/25) of patients in the NAC group survived compared to 20% (5/25) of the controls (p=0.037). In the subset of NAC patients who fulfilled at least one criterion for poor prognosis 5/17 (29%) survived compared to 1/18 (6%). This difference, however, was not statistically significant. The authors also report that fewer NAC than placebo patients developed cerebral edema (40% versus 68%), and fewer NAC NAC patients than placebo required drug control of blood pressure (48 versus 80%). Both comparisons were statistically significant.

i. Reviewer Comments.

1. The rationale behind the NAC administration in APAP OD is to prevent the development of hepatic failure, as appropriately stated in the oral NAC approved indication. The approved oral NAC indication recommends to initiate NAC therapy as soon as possible, and in all cases within 24 hours after the APAP OD. This first primary study was not design to prevent hepatic failure since all patients had advanced hepatic failure at baseline, prior to NAC treatment, and, all patients received NAC i.v. infusions well after the 24 hours of APAP OD. Hence, the results of this study do not provide evidence of i.v. NAC efficacy for the prevention of hepatic failure in APAP OD. Noteworthy, the mortality rate of NAC treated patients, i.e., 52%, may rank among the highest mortality rates reported in APAP OD patients treated with NAC..

2. The additional relevant purpose to present a study as primary (or pivotal), is to provide support of the proposed experimental drug dose-regimen. The proposed Cumberland dose-regimen for its i.v. NAC is composed of three parts, namely, (a) a 60 minute 150 mg/kg loading dose, (b) a 4 hour infusion followed by (c) a 16 hour 100 mg/kg continuous infusion. The NAC i.v. dose-regimen used in this first primary study included a 15 minute 150 mg/kg loading dose, that is, a loading dose administered ——— that the Cumberland proposed loading dose. Thus, the first part of the dose-regimen can not be used to support the sponsor's proposed dosing regimen.

3. As stated, the sponsor has not provided documentation to support the design, patient protection, adequacy, and the results of this placebo-controlled study.

(ii) Brief Summary of the Prospective Protocol Used to Conduct the Next Two Primary Studies (Perry et al, and, Smilkstein et al).

- This Protocol was sponsored by Mead Johnson Pharmaceuticals, the supplier of the NAC i.v. solution. It was finalized in 1983.

  Objectives. (a) to evaluate the safety and efficacy of i.v. NAC in the treatment of patients who have ingested an APAP OD, (b) to compare the safety and efficacy of oral and i.v. NAC given in similar dosing regimens, (c) to obtain PK data on i.v. NAC.

  Patient Sample Size. This protocol planned for an enrolment of approximately 150 patients, with 100 patients required to complete the i.v. dose regimen. NAC PK was planned to be done in 20 patients.

Design. Open, non-randomized, multi-center. The oral NAC information was included in the protocol as "pool" historical data.

I.V. NAC Dosing Regimen. A loading dose of 140 mg/kg followed by 70 mg/kg every 4 h for a total of 13 doses..

Gastric Lavage and Charcoal Administration. All patients should have gastric lavage, and be administered oral activated charcoal.

Inclusion Criteria. "*Patients at any age and sex who present with a history of known or suspected acute ingestion of 7.5 g or more of APAP in adults or 140 mg/k of APAP in children who can be treated with NAC within 24 h time of ingestion of the APAP OD will be entered in the study*"..

Exclusion Criteria. (1) "*any patient who at the time of ingestion of APAP is not known to be within a 2 h range*", (b) "*any patient in whom NAC therapy cannot be initiated within 24 h following APAP OD*", (c) any patient who does not have a toxic APAP level range, (d) any patient known to have NAC hypersensitivity.

"*Statistical Variables*". Comparison of the studied NAC i.v. to the oral (140 mg loading then 70 mg/k every 4 h for a total of 18 doses). Variables include death, maximum serum ASTs, ALTs, PT, bilirubin.

- **H.E. Perry et al. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label, clinical trial. J Pediatr 132:149-152, 1998.**

Design. Open, non-randomized i.v. NAC treatment of APAP OD.

Period of Study. Ten years, i.e., between March 1986 to June 1996. A group of patients who had ingested an APAP OD and had been treated with oral NAC, enrolled in a 7 y period, served as historical controls.

Length of NAC Administration. 52 hours for the i.v. NAC group versus 72 hours in oral NAC group.

Mixed I.V. and Oral Treatment. The report indicates that failure to initiate oral therapy did not preclude to treat these patients with i.v. NAC. Success of oral NAC therapy was defined as no vomiting for 1 h after the initial oral dose.

Intravenous and Oral NAC Dose-Regimen. As described in the above prospective study protocol. All doses were infused for a period of 1 hour.

Summary of Patient Demographics and Results. The investigators treated 25 APAP OD adolescents with i.v. NAC. Twenty nine patients, within the same age range, treated with oral NAC, served as historical controls. Between 88-90% of the treated patients were females. The demographics and time to therapy data are shown in Table I. During the study period, 83 patients were excluded from the trial (*43 because of non-toxic APAP ingestion, 12 with signs of liver failure, 5 for "long-term ingestion", 15 for entry after 24 h of APAP ingestion, 7 for reasons of mixed oral-i.v therapy, 1 patient because apparent ingestion of the APAP in the ER*). The text report states that the charts of 4 treated patients were not found, and they were excluded from the analyses. LFTs in patients who developed severe hepatotoxicity (7-8%) are shown in Tables II-III. The PT, was significantly prolonged in the NAC group.

Table I. Patient characteristics by treatment group

	Intravenous group (n = 25)	Oral group (n = 29)	p Value
Age (yr)	15.5 ± 1.8	15.9 ± 4.1	NS
Gender (% female)	88	90	NS
Treatment delay (hr)	14.4 ± 4.4	10.4 ± 3.7	0.001
Risk categories			NS
High	13	15	
Probable	12	14	

Data are expressed as means ± SD.
NS. Not significant.

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Table II. Peak recorded laboratory values

	Intravenous group (n = 25)	Oral group (n = 29)	p Value
AST (IU/L)	62 (18-3684)	34 (15-10,600)	NS
ALT (IU/L)	82 (11-6906)	42 (13-9840)	NS
Bilirubin (mg/dl)	0.9 (0.3-17.8)	0.9 (0.4-12.1)	NS
PT (sec)	14.2 (12.7-27.5)	15.6 (11.0-57.2)	0.048

Data are expressed as medians with ranges in parentheses.
NS, Not significant.

Table III. Incidence of major outcomes

	Intravenous group (n = 25)	Oral group (n = 29)	p Value
Severe hepatotoxicity	2 (8%)	2 (6.9%)	NS
Coagulopathy	2 (8%)	0	NS
Encephalopathy	0	1 (3.4%)	NS

NS, Not significant.

i. Reviewer Comments.

1. The i.v. NAC dosing regimen used in study differs, markedly, from the i.v. NAC dosing regimen proposed by the sponsor. In this study APAP OD patients had an i.v. loading dose of 140 mg/kg, and then received 70 mg/k every 4 h for a period of 52 h (12 doses). All doses were administered for a period of 1 h. The i.v. dosing in the proposed label starts with a loading dose of 150 mg/k administered in ——— followed by an infusion of 50 mg/k in 4 hours, and a 16 h infusion of 100 mg/k for a total dosing period of 21 h. Hence, the NAC efficacy results of this Perry trial, obtained with a different initial load and intermittent dosing for a total treatment period of 52 h, cannot be extrapolated to support efficacy of the sponsors proposed initial load, 50 mg/k for 4 and continuous 16 h dosing for a total 21 h treatment period..

2. The potential administration of oral NAC prior to the i.v. NAC dosing in many of the patients is an additional variable that further confounds the efficacy results of this study.

3. The efficacy analyses is incomplete, for it does exclude treated patients.

- **MJ Smilkstein et al. Acetaminophen overdose: a 48 h intravenous N-acetylcysteine treatment protocol. Ann Emerg Med 20:1058-1063, 1991.**

Design, Dosing Regimen and Length of I.V. NAC Administration. Design, NAC loading dose and intermittent i.v administration were the same as described in Perry study (*both studies conducted under identical protocol*). The only difference was in the shorter period of NAC treatment, i.e., 48 h.

Summary of Patient Demographics and Results. Two hundred twenty three APAP OD patients entered the study. The authors state that 179 met the inclusion criteria. Reasons for exclusion were low acetaminophen plasma concentrations (N=23), unknown time of ingestion (N=10), less than 12 doses of i.v. NAC (N=6), more than 14 i.v. NAC doses (N=1), insufficient LFT to determine outcome (N=2),NAC treatment started after 24 h of APAP OD (N=1), 1 patient with rhabdomyolysis inconsistent with APAP OD. Patients were grouped according to a standard acetaminophen plasma levels normogram in "possible risk" group (200 μg/ml), "probable risk" group (between 200-300 μg/ml), and "high risk" group (above 300 μg/ml). As seen in Table 1, the majority of patients fell in the "probable to high risk" group. Patients were similarly grouped according to time of initiation of i.v. NAC therapy after APAP OD, i.e., ≤10 h or 10-24 h. The majority of patients were treated after a 10 h ingestion period (59%). The majority of patients were women (79%) with a median age of 21 years (56% between the ages of 10-20 y). Six of the 179 treated patients were less than 6 y old.

Table 1 shows that there was a statistical difference in the levels of hepatic ALTs and ASTs between patients with high plasma APAP concentrations treated ≤10 h after the OD and patients treated between 10-24 h after the OD. These latter patients had significantly higher liver enzymes. There were a total of 5 deaths in the 223 patients entered in the study (1 suicide subsequent to the APAP OD). Two deaths occurred in the 179 analyzed patients; both deaths due to complications of acute hepatic failure.

Note from Reviewer: Tables were scanned from submitted report copies. Some details may not be legible.

TABLE 1. *Aminotransferase analysis by risk group and delay to treatment*

	Treatment Delay		
	0 to 10 Hours*	10 to 24 Hours†	P‡
Group 1 (Possible Risk)			
Mean peak AST (IU/L)	145.3 ± 513.8	444.9 ± 1,515.7	.398
Mean peak ALT (IU/L)	118.9 ± 374.7	401.7 ± 1,195.2	.311
Median peak AST (IU/L)	29	30	.978
Median peak ALT (IU/L)	24	27	1.0
No. of patients with AST or ALT of more than 1,000 IU/L (%)	1/23 (4.3%)	1/21 (4.8%)	1.0
Group 2 (Probable Risk)			
Mean peak AST (IU/L)	162.3 ± 51.8	1,245.3 ± 284.5	< .0005
Mean peak ALT (IU/L)	282.8 ± 77.9	1,408.0 ± 300.5	< .0005
Median peak AST (IU/L)	28.5	80	.0009
Median peak ALT (IU/L)	25	120	.0014
No. of cases with AST or ALT of more than 1,000 IU/L (%)	5/50 (10%)	23/85 (27.1%)	.032
Group 3 (High Risk)			
Mean peak AST (IU/L)	99.5 ± 39.9	1,801.8 ± 453.3	< .0005
Mean peak ALT (IU/L)	196.2 ± 143.7	1,974.4 ± 472.3	< .0005
Median peak AST (IU/L)	28.5	110	.002
Median peak ALT (IU/L)	30.5	170	.0007
No. of cases with AST or ALT of more than 1,000 IU/L (%)	1/24 (4.2%)	16/50 (32%)	.018

*There was no statistical difference in any outcome measure between groups 1, 2, and 3 in patients treated within ten hours.
†All outcome measures progressively worsened with increasing risk group; mean peak AST ($P = .0008$) and ALT ($P = .0002$), median peak AST ($P < .0001$) and ALT ($P = .0008$), proportion of cases with AST or ALT of more than 1,000 IU/L ($P = .028$).
‡Ten to ten hours vs ten to 24 hours.

In the next Table 2, the authors compare the "hepatotoxicity" found in this study (48 h intermittent i.v.NAC treatment) and historical data from two other selected publications of i,v, NAC and oral NAC therapy reports.

TABLE 2. *Comparison of hepatotoxicity with other N-acetylcysteine protocols*

Treatment Delay	48-Hour IV (%)	20-Hour IV (%)	72-Hour Oral (%)
Group 2 (Probable Risk)			
0–10 hours	5/50 (10) [3–22%]	1/62 (1.6) [0–9%]	32/527 (6.1) [4–8%]
10–24 hours	23/85 (27.1) [18–38%]	30/38 (52.6) [36–69%]	247/935 (26.4) [24–30%]
Group 3 (High Risk)			
0–10 hours	1/24 (4.2) [0–21%]	1/33 (3) [0–16%]	17/206 (8.3) [5–13%]
10–24 hours	16/50 (32) [19–47%]	18/27 (67) [46–83%]	199/578 (34.4) [30–37%]
16–24 hours	11/19 (57.9) [34–80%]	9/11 (82) [48–98%]	116/283 (41) [35–47%]

Values given are number of cases (%) [95% confidence intervals] with AST or ALT of more than 1,000 IU/L.

i. Reviewer Comments.

1. My previous comments of the Perry et al. study, related to the dosing regimen differences, apply to this Smilkstein et al study. The efficacy results in APAP OD patients, obtained with an i.v. NAC dose regimen of 140 mg/k load dose, intermittent 70 mg/k administration and 48 length of therapy, cannot be extrapolated to an i.v. NAC regimen of 150 mg/k loading dose, 4 h of 50 mg/k, and a continuous 16 h therapy of 100 mg/k.

2. The efficacy results are further confounded by the exclusion of 7 NAC-treated patients who were excluded from the trial, and other unaccounted exclusions.

3. Noteworthy are the authors comments on the comparison of hepatotoxicity found in this study and hepatotoxicity described in historical reports. The authors state that "*Unfortunately, valid statistical comparison with historical controls is precluded by the unavailability of prior raw data and by the possibility of difference in numerous confounding variables between the study samples. As a result, further study is needed to accurately determine efficacy of different treatment, particularly in the most problematic patients in group 3 first treated more than 16 h after OD*".

- **T.E. Oh and Gillian M Shenfield. Intravenous N-acetylcysteine for paracetamol poisoning. Med J Aust 1:664-665, 1980.**

NAC Dosing Regimen and Demographics. This is a one page report of eleven APAP OD patients treated with open-label i.v.-NAC. NAC i.v., given first as a 150 mg/k load, followed by 4 h 50 mg/k dose and 8 h continuous infusion, was administered for a total of 13 hours. There was no mention time of loading-dose administration. All patients underwent gastric lavage and were given oral activated charcoal prior to the i.v. NAC therapy. The following Table 1 lists patents age, sex, paracetamol plasma concentrations, and liver transaminases on admission. As seen in the table, 91% of the patients were females. Serum transaminases, bilirubin levels, and PT ratio in Patient 1 are diagnostic of hepatic failure. The authors report recovery of all patients..

TABLE 1

Details of Patients with Paracetamol Poisoning Treated with Intravenous N-Acetylcysteine

Patient	Age (Years)	Sex	Ingestion-Treatment Interval (Hours)	Initial Paracetamol Level (mg/L)	Maximum AST u/L	Maximum Bilirubin Level (μmol/L)	Prothrombin Ratio
1 ..	28	F	20	[illegible]	7140	67	2.5
2 ..	22	F	8	[illegible]	28	9	1.1
3 ..	15	F	10	[illegible]	102	18	1.0
4 ..	18	F	8	[illegible]	39	9	1.0
5 ..	21	F	6	[illegible]	47	11	1.0
6 ..	17	F	8	[illegible]	30	20	1.1
7 ..	34	F	8	[illegible]	30	10	1.0
8 ..	52	F	4	[illegible]	28	9	1.0
9 ..	57	F	5	[illegible]	30	8	1.1
10 ..	34	F	3	[illegible]	33	10	1.0
11 ..	61	M	7	[illegible]	28	11	1.1

M=male. F=female. AST=Aspartate aminotransferase.

i. Reviewer Comments.

1. This 11 patient report is an interest observation in female APAP OD, but constitute little evidence (if any) of continuous i.v. NAC efficacy for APAP OD . Further, the i.v. NAC dosing regimen does not specify time of loading dose administration, and the continuous i.v. phase was administered for 8 h only, instead of the proposed 16 h submitted in the label.

- **LF Prescott. Treatment of severe acetaminophen poisoning with intravenous acetylcysteine. Ann Intern Med 141:386-389, 1981.**

Design. The author compared the efficacy of 100 patients who ingested APAP OD and were treated with i.v. NAC, cysteine, or methionine given intravenously, and 50 patients who received supportive therapy.

Objective. The main objective was to demonstrate the that interval between the APAP OD and initiation of the i.v. NAC therapy, i.e., < or > than 8-10 h is relevant in the prevention of liver failure due to APAP OD.

Dosing Regimen of the i.v. NAC. The i.v. NAC dosing regimen is shown in Table 1.

Table 1.—Intravenous Acetylcysteine for Acetaminophen Poisoning

Dose of Acetylcysteine, mg/kg*	Volume of 5% Dextrose, mL	Duration of Infusion
150	200	15 min
50	500	4 hr
50	500	8 hr
50	500	8 hr

*Total dose, 300 mg/kg in 20 hours, 15 minutes.

Patient Demographics. All patients were diagnosed as having APAP OD by measurements in the normogram of the APAP plasma levels. The mean age of patients was 33 y (13 to 82 y). There were 42 males and 58 females. NAC i.v. was given as a 20% sterile aqueous solution.

Results. Tables 2, 3 summarize the results Basically, there was a noticeable difference between the proportion of patients with liver damage among those treated with i.v. NAC within 10 h after the APAP OD (2%) and the proportion of liver damage among those treated with i.v. NAC after

10h post OD. Similar trends were observed in patients treated with i.v. cysteine or methionine..

Table 2.—Intravenous Acetylcysteine Treatment as Compared With Supportive Therapy in Patients With Severe Acetaminophen Poisoning*

Mode of Treatment	No. of Patients	Mean Maximum ALT Activity,† IU/L	Mean Maximum Bilirubin Concentration, mg/dL	Mean Maximum Prothrombin Time Ratio	No. (%) With Severe Liver Damage‡
Acetylcysteine within 10 hr	62	113	0.9	1.3	1 (2)
Acetylcysteine within 10 to 24 hr	38	3,814	3.4	1.9	20 (53)
Supportive therapy	57	>2,022	3.3	1.9	33 (58)

*Data from Prescott et al.[4]
†Alanine aminotransferase is ALT.
‡Liver damage is ALT or aspartate aminotransferase activity greater than 1,000 IU/L.

Table 3.—Liver Damage in High-Risk* Patients With Acetaminophen Poisoning Receiving Supportive Therapy and in High-Risk Patients Receiving Intravenous Acetylcysteine†

Mode of Treatment	No. of Patients	Mean Maximum ALT Activity,‡ IU/L	Mean Maximum Bilirubin Concentration, mg/dL	Mean Maximum Prothrombin Time Ratio	No. (%) With Severe Liver Damage§
Acetylcysteine within 10 hr	33	185	0.9	1.3	1 (3)
Acetylcysteine within 10 to 24 hr	27	4,919	4.2	2.1	18 (67)
Supportive therapy	28	>3,186	5.2	2.3	25 (89)

*Plasma acetaminophen above a semilogarithmic plot of 300 μg/mL at 4 hours and 45 μg/mL at 15 hours.
†Data from Prescott et al.[4]
‡Alanine aminotransferase is ALT.
§Liver damage is ALT or aspartate aminotransferase activity greater than 1,000 IU/L.

i. Reviewer Comments.

1. This trial, one of the first trials with i.v. continuous NAC infusion in APAP OD, offers relevant information on the need to initiate NAC therapy promptly, i.e., within 10 h after the OD. The loading dose, given here in 15 minutes, and the two 8 h i.v. infusion periods, constitute differences that make an extrapolation to the sponsor's proposed ——— load and continuous 16 h infusion difficult to interpret. The following questions remain: Would the results have been the same if the loading dose of 150 mg/k would have been spread for——— ? Were the two 8 h infusion periods consecutive in all patients, or in some patients? As commented by Smilkstein et al in his

publication, interpretation of this historical information without corroboration of raw data precludes a valid interpretation of efficacy results.

2. Noteworthy, the difference in the proportion of NAC patients with biochemical liver damage treated after the 10-24 h APAP OD was high (67%), and similar to the proportion of patients with severe liver damage treated with supportive therapy after the same 10-24 h post-APAP OD..

- **Interim Analysis of CMAX Study No CM8801.**

This interim analysis (IA), was performed by ———— (*contracted by the sponsor, Cumberland Pharmaceuticals, Inc*). The IA was completed on April 2001. It included patients enrolled in Study CM8801 from May 6 1999 to March 30, 2001. All 6 centers enlisted in Study CM8801 were located in Australia

Protocol. One page protocol submitted on Page 180, Vol. 1.8.1 (Vol. 1.9).

Aim. *"To determine the incidence of adverse reactions due to i.v. NAC is significantly less when a 60 minute infusion rate for the initial dose is compared with the standard infusion for the initial dose of over 15 minutes. All patients will be carefully monitored for efficacy in both treatment arms of the study".*

Inclusion (Criteria). All patients that present to the hospitals with paracetamol poisoning that requires the administration of NAC.

Exclusion (Criteria). Patients with known hypersensitivity to NAC will be excluded.

Design. Multi-center, randomized, "prospective trail".

Planned Patient Size. A total of 500 patients randomized to two groups: (a) 60 minutes 150 mg/k NAC i.v. loading dose or (b) 15 minutes 150 mg/k NAC i.v. loading dose. All patients will subsequent to the loading dose receive.4h of 50 mg/k, followed by a continuous i.v. infusion of 100 mg/k for 16 h.

Efficacy Endpoints. There were no established efficacy endpoints. There is one sentence in the protocol stating that *efficacy will be assessed by analysis of serum AST, ALT and International Normalized Ratio (INR). Blood for these tests will be drawn at baseline, and 12 hours intervals (4 samples)*. The protocol states

that "*if there is any preliminary data that indicates lack of efficacy of the treatment arm the study will be terminated immediately*".

- Patients and Results Observed in the IA of Study CM8801..

(a) The IA performed included 99 patients. The sponsor excluded 3 patients for the following reasons (*scanned from the edr*). Hence, the patient data included 96 patients.

Following the recording of these data, it was realized that Patient 17 and Patient 49 both entered the study after the nominal cut-off date and thus were incorrectly allocated a patient code. As such, data from Patient 17 and Patient 49 have not been included in the data listings or this interim analysis. One patient (Patient 24) was not formally randomized in accordance with protocol procedures (refer to Section 6.2) and as such data from this patient was also not included in the data listings or this interim analysis.

The following sponsor's Table 5 shows the breakdown of the two groups. the data included 61 patients given 15' NAC load and 35 patients administered 60' NAC load. Seventy three percent (70/96) were females.

Table 5: Mean Demographic Data by Gender and Treatment

Treatment	Mean age (yrs)	Mean Weight (kg)
15-minute (n=61)	32	66.87
For 15-minute treatment Male (n=12): Female (n=49):	 36 31	 81.71 62.94
60-minute (n=35)	29	69.05
For 60-minute treatment Male (n=14): Female (n=21):	 31 28	 87.36 59.20

Eleven patients did not complete the NAC therapy, i.e., 4 in the 60' group and 7 in the 15' group. The reasons for premature discontinuations are shown in the next sponsor's Table 12.2.1.

Table 12.2.1 Discontinued Patients

Patient Number	Site Number	Treatment	Reason for Patient Discontinuation
08	01	60-min	Patient absconded from hospital.
21	02	15-min	This patient was withdrawn due to a low paracetamol level, which was below warranting treatment with NAC.
34	02	60-min	This patient was withdrawn due to an adverse event.
36	02	15-min	This patient was withdrawn due to a low paracetamol level at 4 hours, which was below NAC treatemnt level.
38	02	15-min	NAC infusion was not indicated as originally thought.
40	02	15-min	Patient transferred to psychiatric hospital, liver function values normal.
56	03	60-min	Infusion ceased and pateint was withdrawn when liver function values improved.
64	02	60-min	Patient transferred to adolescent unit.
71	02	15-min	This patient was withdrawn due to a low paracetamol level, which was below warranting treatment with NAC.
86	05	15-min	NAC infusion no longer clinically indicated.
99	06	15-min	This patient was withdrawn due to an adverse event.

(b) *Efficacy*. ALT values were available for 95 patients, AST for 55 and INR for 72. The sponsor states that there were no differences in LFTs between groups based on the analysis of maximum measured ALT using a non-parametric Wilcoxon test (p=0.18). The range ALT levels are shown in the next table (*scanned from edr*).

		ALT subject max level	
		No. of subjects in range	
Breaks	Range	15-min, N=61	60-min, N=34
0	Normal: 0-55	48	22
55	Elevated: 56-150	7	3
150	Lesser hepatic injury: 151-1000	3	5
1000	Hepatotoxicity: >1000	3	4
Total N		61	34
	Unknown	0	1
	%Normal/Known	79%	65%
	%Elevated/Known	11%	9%
	%Injury/Known	5%	15%
	%Toxicity/Known	5%	12%
	%Unknown	0%	3%

The sponsor states the following about the levels of hepatotoxicity (*the relevant index to assess NAC efficacy as preventive antidote*) (*copied and unedited*):

The observed rates of hepatotoxicity for the two treatment groups were 5% (3 patients out of 61) for the 15-min treatment group and 12% (4 patients out of 34) for the 60-min treatment group. With the relatively small numbers of patients involved in this interim analysis, the difference between the hepatotoxicity rate in the two groups is not statistically significant (the difference is 7%, with a standard error of 6%).

Toxicity is effected by the dosage of paracetamol consumed and the time between ingestion of the paracetamol and administration of NAC.

Graphs of maximum measured ALT, and log (ALT), against maximum paracetamol concentration did not indicate any strong relation between maximum paracetamol concentration and maximum measured ALT for either treatment group (refer to Section 10.3). The R-squared value for fitting a regression of maximum measured ALT on maximum measured paracetamol is less than 0.1, on both linear and log scales, with the estimate for the slope being negative.

In reference to the above efficacy results, Cumberland concludes the following (*copied and unedited*)

Previous studies have shown that hepatotoxicity is rare in patients who receive NAC treatment within 8 hours of paracetamol exposure (Smilkstein, Knapp, et al. 1988). Once 8 hours has elapsed in patients with at risk paracetamol concentrations, sufficient NAPQI has been produced to cause some hepatic injury. Thus a transaminase rise in patients who present later than 8 hours is not useful in determining the relative efficacy of the two treatment protocols.

In this study there were 29 patients for whom the only listed ingestion of paracetamol is within 8 hours of the start of NAC administration (18 with 15-min initial infusion time, 11 with 60-min initial infusion time). None of these patients were among the seven who had measured ALT values above 1000 U/L. These seven were all known to have had a lapse of at least 8 hours since ingestion of paracetamol (with one patient ingesting additional paracetamol within 8 hours of NAC start time). This is a known risk factor for the development of hepatotoxicity.

Given the sample sizes and the nature of the data, it was determined by the clinical investigators at [redacted] in conjunction with the Consultant Statistician, that any further analysis on hepatotoxicity would not provide meaningful information.

i. **Reviewer Comments.**

1. This interim analysis, encompassing only 20 % of the 500 planned patient population, has no relevant efficacy results. The absence of an active comparator, e.g., oral NAC or i.v. methionine, is an indispensable factor missing in the interpretation of the data.

2. Noteworthy, in spite that 70 % of patients treated with i.v. NAC received the antidote >10 h after the APAP OD, only 6 % of patients developed ALTs ≥1000 IU, i.e., range of hepatic failure.

3. The validity of the prospective randomization may be in doubt, for of the 96 consecutive patients allocated to the two groups, 68% were allocated to the 15' loading dose versus 32% to the 60' loading dose. The Division of Biometrics (Dr. Tom Permutt) is reviewing this and other statistical issues.

D. Efficacy Conclusions

The sponsor submitted six "Primary Studies". Five of the studies were historical reports (publications). Of these five historical reports, the study by Keays et al. was the only placebo-controlled study. This study, however, was designed to study fulminant hepatic failure due to APAP OD. Indeed, all 50 patients enrolled in this study had hepatic failure at

baseline and the authors reported a 52% mortality rate in patients treated with intravenous NAC, an unacceptable rate for APAP OD patients treated with NAC. Hence, this study is not of use to address the issue of i.v. NAC efficacy in the *prevention* of hepatic failure due to APAP OD. Further, the length of the iv. loading dose in the Keays study, 15 minutes, differs from the specific length of loading time, [redacted] included in the proposed label. Two other published reports, both conducted under identical Mead Johnson protocol in the 1980's, include some efficacy of i.v. NAC in APAP OD (Perry et al and Smilkstein et al). Both studies were open-label, and, the comparisons were made against prior historical efficacy data obtained with oral NAC therapy. As importantly, the intravenous NAC dosing regimen in both studies, differed from the NAC intravenous regimen proposed by the sponsor, i.e. [redacted]. A similar problem with dosing regimens were observed in the primary studies reported by Oh and Prescott.. The study by Oh and Sheinfeld was a one page report of 11 cases treated in a medical center (no control treatment). The sponsor submitted an IA of a study designed to assess safety two different i.v. loading dose periods, 15 minutes versus 60 minutes. The protocol planned for 500 patients; the IA analysis included <20% of the planned patient population (96 patients), and did not reveal any difference in efficacy.

Based on my review of the submitted primary studies, I conclude that there is no substantial evidence of effectiveness to support approval of the sponsor's proposed regimen of continuous intravenous NAC therapy, to be used for the appropriate indication [redacted].

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

My review of the submitted safety information leads me to conclude that the i.v. NAC safety is acceptable. As it will be described, there are some rather serious risks in the use of i.v. NAC as relates to anaphylactoid reactions. Although these AEs have been observed with both, oral and i.v. NAC administration, they appear to occur more frequently with i.v. NAC. The anaphylactic reactions to NAC appear to be more serious with i.v. administration. A few deaths have been associated with apparently large doses of i.v. NAC. Exposure to the drug, listing of AEs in primary studies and the Rocky Mountain Poison Center compilation will be shown in the next sections.

B. Description of Patient Exposure

The following sponsor's table, taken from the ISS, Page 141, Vol 1.8.3 (or Vol 1.11) shows the exposure to i.v. NAC in APAP OD reported in the primary studies, and few other publications.

Table 19 **Exposure to Iv NAC: Published Clinical Studies With an Iv NAC Dosing Regimen Similar to Proposed Regimen, Acetaminophen Overdose**

Study Design/ Reference	Dose Regimen	Number of Studies	Number of Patients
Randomized, controlled (Keays, 1991)	LD: 150 mg/kg over 15 minutes MD: 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours	1	25
Open Label (Perry, 1998; Smilkstein, 1991; Oh, 1980; Prescott, 1981; Prescott, 1989; Harrison, 1991; Prescott, 1977; and Beckett, 1990)	LD: 140 mg/kg over 60 minutes MD: 12 doses of 70 mg/kg every 4 hours	2	204
	LD: 150 mg/kg over 15 minutes MD: 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours	6	166
Retrospective (Prescott, 1979; Chan, 1994; Lifshitz, 2000; Harrison, 1990; Schmidt, 2001; and Chan, 1996)	LD: 150 mg/kg over 30 minutes MD: 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours	1	41
	LD: 150 mg/kg over 20 minutes MD: 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours	1	92
	LD: 150 mg/kg over 15 minutes MD: 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours	4	712

C. Methods and Specific Findings of Safety Review

The sponsor submitted safety data from the IA of study CM8011, some information from the publications or 5 historical data submitted as primary studies (not documented), data from publications on the NAC use for other indications (septic shock, renal transplant, stroke), and review boards on some patients, who were discontinued from these studies due to NAC related AEs, and a summary report on the medical literature regarding safety of i.v. NAC from the Rocky Mountain Poison and Drug Center (Denver, CO) dated 12/27/2001.

Deaths. The next sponsor's Table 45, Page 195, Vol. 1.8.3 (Vol 1.11) lists deaths that occurred in trial reported in the literature.

Table 45 Deaths Reported in Iv NAC Published Clinical Studies by Dosing Regimen: Acetaminophen Overdose

Dosing Regimen	Number of Deaths NAC	Number of Deaths Other	Cause of Death	Related to NAC	Reference
Proposed Regimen	13	20	Not reported	Not reported	Keays, 1991
	5	0	APAP overdose	No	Smilkstein, 1991
	1	0	Suicide	No	
	1	0	Adult respiratory distress syndrome and anoxic brain injury after ingestion of malathion	No	
	2	4	Hepatic failure	No	Prescott, 1981
Other Regimens					
	15	33	Hepatic failure	No	Harisson, 1990
	1	0	Circulatory collapse	Related	Anonymous, 1990
	10	0	Not given	Not reported	Harrison, 1991
	1	0	Iatrogenic overdose (2.5 and 6.0 times the normal loading dosage)	Related	Mant, 1984
	1	0	Iatrogenic overdose (10 times the normal loading dosage)	Related	Mant, 1984
	2	0	Not reported	Not reported	Buckley, 1991

AEs Tabulated in the IA of CM8801.

The following sponsor's Table 10.2.1.3 shows the proportion of patients with 1 or more AEs in the 15' and 60 ' group. No differences were observed between the two group of patients (*scanned from edr*).

Table 10.2.1.3 Adverse Events Incidence by Patient

NUMBER (%) OF PATIENTS WITH ADVERSE EVENTS			
TREATMENT NUMBER OF PATIENTS	15-min n=61	60-min n=35	p-value
With an Adverse Event	49 (80 %)	22 (63 %)	ND
With a drug-related Adverse Event [a]	34 (56 %)	15 (43 %)	0.22
With a moderate or severe drug-related Adverse Event [b]	22 (36 %)	11 (31 %)	0.65
With a severe drug-related Adverse Event [c]	1 (2 %)	1 (3 %)	0.69
With a serious Adverse Event	0 (0%)	0 (0%)	ND
With an Adverse Event resulting in discontinuation of study treatment	1 (2%)	1 (2%)	ND

With a drug-related Adverse Event [a] occurring within the first 2 hours after dose administration	28 (46 %)	14 (40 %)	0.57
With a moderate or severe drug-related Adverse Event [b] occurring within the first 2 hours after dose administration	22 (36 %)	10 (29 %)	0.45
With a severe drug-related Adverse Event [c] occurring within the first 2 hours after dose administration	1 (2 %)	1 (3 %)	0.69

AEs Related to NAC. The following sponsor Table 10.2.1.2 displays the proportion of patients who AEs related to the administration of i.v. NAC. As seen, almost 50% in each group had AEs related to the NAC administration. Anaphylactoid reactions were the most drug-related AEs. In many instances, the i.v. NAC infusion had to be interrupted to attend to the drug-related AEs. These AEs occurred in 10 of the 96 patients.

Table 10.2.1.2 Drug-Related On-Study Adverse Events Occurrence

NUMBER (%) OF PATIENTS[a] WITH ADVERSE EVENTS DEEMED TO BE DRUG-RELATED WITHIN THE FIRST 2 HOURS FOLLOWING DOSE ADMINISTRATION							
TREATMENT NUMBER OF PATIENTS	**15-min n= 61**				**60-min n=35**		
Number of patients with one or more Adverse Events deemed to be Drug-related[a] within the first 2 hours following commencement of study treatment	28 (46 % of patients in 15-min group)				14 (46 % of patients in 60-min group)		
Body as a Whole	15 (54 %)				7 (50 %)		
	Unknown	Mild	Mod	Severe	Mild	Mod	Severe
Anaphylactoid reaction	2	4	7	1	2	4	1
Chest pain		1					
Other			1				
Cardiovascular	4 (14 %)				2 (14 %)		
	Unknown	Mild	Mod	Severe	Mild	Mod	Severe
Vasodilitation			1		2		
Tachycardia		2	1				
Digestive	13 (46 %)				4 (29 %)		
	Unknown	Mild	Mod	Severe	Mild	Mod	Severe
Nausea	1		6				
Vomit			10			4	
Respiratory	1 (4 %)				1 (7 %)		
	Unknown	Mild	Mod	Severe	Mild	Mod	Severe
Pharyngitis			1				
Laryngismus (throat tightness)					1		
Skin	2 (7%)				2 (14%)		
	Unknown	Mild	Mod	Severe	Mild	Mod	Severe
Rash		1			2		
Pruritus		1					
Special Senses	1 (4%)				0 (0%)		
	Unknown	Mild	Mod	Severe	Mild	Mod	Severe
Ear Pain			1				

Tabular Listing of AEs related to Intravenous NAC Provided by the Rocky Mountain Poison Center (RMPC) in Denver, CO. The next Table 1, provided to the sponsor by the RMPC, illustrates the proportion of APAP OD patients who developed NAC-related AEs, in controlled and

uncontrolled studies. The RMPC notes that it excluded historical information considered inadequate. The final list, shown in the table, displays data of 427 AEs which occurred in 254 (12%) of 1040 patients. Overall, anaphylacoid reactions were the most frequent reported AE.

Table 1: Adverse Events by Body System Classification

Body System Classification	Adverse Event Occurrences	% of All Adverse Event Occurrences	Frequency in Patients with Safety Monitoring (n=2040)
Body as a Whole & Combinations			
Allergic Reaction	1	0.23%	0.05%
Anaphylactic Shock	2	0.47%	0.10%
Death	3	0.70%	0.15%
Edema - General	1	0.23%	0.05%
Fever	3	0.70%	0.15%
Injection Site Reaction	1	0.23%	0.05%
Urticaria	34	7.96%	1.67%
Vasodilatation & Rash	30	7.03%	1.47%
Vasodilatation, Rash, & Pruritus	42	9.84%	2.06%
Vasodilatation with Pruritus	3	0.70%	0.15%
Cardiovascular System			
Hypertension	3	0.70%	0.15%
Hypotension	16	3.75%	0.78%
Infarct Myocardial	4	0.94%	0.20%
Palpations & Chest Pain	1	0.23%	0.05%
Syncope	13	3.04%	0.64%
Tachycardia	3	0.70%	0.15%
Thrombosis	1	0.23%	0.05%
Vasodilatation	28	6.56%	1.37%
Digestive System			
Dyspepsia	5	1.17%	0.24%
Nausea	43	10.07%	2.11%
Vomiting	15	3.51%	0.74%
Metabolic & Nutritional Disorders			
Cyanosis	2	0.47%	0.10%
Nervous System			
Abnormal Thinking (Dysphoria)	8	1.87%	0.39%
Dizziness	1	0.23%	0.05%
Gait Disturbances	5	1.17%	0.24%
Seizure (epilepticus)	2	0.47%	0.10%
Taste Perversion – Metallic Taste	3	0.70%	0.15%
Respiratory System			
Apnea	1	0.23%	0.05%
Asthma- bronchial	1	0.23%	0.05%
Bronchospasm	25	5.85%	1.23%
Coughing	18	4.22%	0.88%
Dyspnea	11	2.58%	0.54%
Skin & Appendages			
Angioedema	33	7.73%	1.62%
Erythema	3	0.70%	0.15%
Facial Erythema	5	1.17%	0.24%
Palmar Erythema	6	1.41%	0.29%
Pruritus	5	1.17%	0.24%
Pruritus & Rash	7	1.64%	0.34%
Rash	21	4.92%	1.03%
Sweating	6	1.41%	0.29%
Special Senses			
Blindness – Cortical	1	0.23%	0.05%
Pain - Eye	11	2.58%	0.54%
Total	427	100%	20.93%

D. Adequacy of Safety Testing

The safety data from the IA of Study CM8801, the only prospectively monitored data, includes only >20% of the planned patient population. Further, the safety data included in the historical publications lacks objective documentation to corroborate the reported findings (*as* is *the case with the efficacy data*).

E. Summary of Critical Safety Findings and Limitations of Data

Any proposed label for the use of intravenous NAC should include two *PRECAUTIONS*:. (a) serious anaphylactoid reactions may occur with administration of NAC by the parenteral route. Patients who have a medical history of asthma, allergic skin reactions should not be given the antidote, or be given by the oral route (b) NAC intravenous treatment should not exceed the recommended doses. A few deaths have been reported with doses exceeding the reported recommended limits.

VIII. Dosing, Regimen, and Administration Issues

This is perhaps the most deficient element of the submission. Only one of the six submitted primary studies (IA of CM8801) had the totality of the i.v. NAC dosing phases proposed in the label, i.e., [redacted] 150 mg/k loading dose, followed by 4 h 50 mg/k infusion, followed by 16 h 100 mg/k continuous infusion. Lamentably, the IA includes only 20% of prospectively planned patient population, the design was not aimed to demonstrate efficacy, there were only 11 patients eligible to assess efficacy in the IA at the proposed dosing regimen, and the efficacy results show no difference with a comparable dosing regimen.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor did not include data on special populations (Section 53, Vol. 11)

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The sponsor did not include data on special populations (Section 53, Vol. 11)

C. Evaluation of Pediatric Program

The relevant issues of the provided pediatric information are the following:

- The sponsor states that [redacted] The sponsor made reference to two publications. One of them is the previously described study by Perry in 25 adolescents. The other included 3 patients .

- There were 15 deaths among 104 pediatric patients reported in the literature associated with the use of i.v.NAC. One infant died 3 hours after birth; the mother had been treated with i.v. NAC before and, apparently, during delivery, for APAP OD. There were 10 deaths in premature infants. The majority of these premature infants had serious concomitant diseases. One child died from what the sponsor described as an excessive i.v. NAC dose. During the infusion, the child became cyanotic and never recovered from circulatory collapse.

- There were two pediatric cases of seizure associated with the administration of i.v. NAC for APAP OD.

- AEs with i.v. NAC reported in pediatric patients are similar to those described in the adult population. Anaphylactoid reactions, sometimes severe, are the most frequent AEs (bronchospasm, asthma excacerbation, urticaria).

i. Reviewer Comments.

Administration of i.v. NAC in some pediatric populations appear to be associated with serious AEs (almost 15% mortality). Given the scarcity of efficacy data provided by the sponsor in pediatric populations <12 y, there should be great caution in administering i.v. NAC in this pediatric group.

D. Comments on Data Available or Needed in Other Populations

There is a need to have efficacy and safety data on i.v. NAC in patients with APAP OD who have ethanol-induced cirrhosis. Efficacy and safety data are also needed in the geriatric population.

X. Conclusions and Recommendations

A. Conclusions

Only 3 of the 6 Primary Studies submitted by the sponsor were designed to show evidence of efficacy with the use i.v. NAC as antidote to prevent hepatic failure from APAP OD. The Prescott (Study 5), was perhaps the best of the submitted studies for it included more than 25 patients in each arm, there were comparisons to active-active controls and to supportive treatment. The study revealed that among APAP OD patients treated with i.v. NAC after 10 h from the OD there was a 53% of hepatic failure (mean serum ALT >3000 IU, serum bilirubin 3.4 mg/dl). This very high proportion of hepatic failure was not different from the 58% of hepatic failure observed in control patients treated with supportive treatments (serum ALT >2000, serum bilirubin 3.3 mg/dl). This study appears to suggest a narrow therapeutic range of the i.v. NAC. The other two Primary Studies revealed some efficacy as compared to oral NAC historical data. None of the patients enrolled in the Primary Studies received the i.v. NAC dosing regimen proposed in the label. The lack of substantial evidence of effectiveness based on adequate and well-controlled studies plus the potential of anaphylactoid AEs, sometimes severe, does not provide an acceptable risk benefit ratio for i.v. NAC approval.

B. Recommendations

In view of the lack of adequate and well-controlled studies showing substantial evidence of effectiveness with the proposed i.v. NAC dosing regimen, and the rather high risk/benefit ratio, I do not recommend approval of the proposed i.v. NAC dosing regimen for the prevention of hepatic failure in APAP OD.

I recommend to convey the following to the sponsor:

1. [redacted]

2. [redacted]

3. Address the CMC and microbiological deficiencies.

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/s/

Robert Prizont
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MEDICAL OFFICER