CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-539

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION--ADDENDUM

CLINICAL STUDIES

NDA/Serial Number:	21-539
Drug Name:	Acetadote (Acetylcysteine Injection)
Indication(s):	Antidote for potentially hepatotoxic quantity of acetaminophen
Applicant:	Cumberland Pharmaceuticals, Inc.
Date(s):	July 21, 2003
Review Priority:	Resubmission; 6-month review
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Lisa Kammerman, Ph.D.
Medical Division:	Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Clinical Team:	Medical reviewer: Robert Prizont, M.D.
Project Manager:	Paul Levine, Jr.

Keywords: **Clinical studies, meta-analysis, historical data, observational data, labeling**

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

As stated in my review dated January 7, 2004 the submission does not provide substantial evidence of safety and efficacy for N-acetylcysteine injection (I.V. acetylcysteine).

If the medical division decides to approve the product based on the information from this submission, I recommend the following information for the Clinical Studies section of labeling.

CMAX CM8801

The Clinical Studies section of the label needs to report the results from CMAX CM8801, which is the only prospectively randomized clinical study contained in the submission. The study provides data for the hepatotoxicity endpoint.

Because CMAX CM8801 was a safety study designed to compare rates of anaphylactoid reactions between a loading dose infused over 15 minutes versus a loading dose infused over 60 minutes, the Clinical Studies section needs to report the results for this endpoint. Anaphylactoid reactions are a major safety concern for the I.V. formulation. The rates of anaphylactoid reactions within the first two hours of start of treatment were 18% (15-minutes) and 14% (60-minutes).

In the Adverse Reaction section, the anaphylactoid reaction results are not obvious to the reader because of their location in the table. Moreover, the table is followed by "Drug-related adverse events occurring within 2 hours of initiation of treatment were observed to be similar in the 15-minute loading dose regimen compared to the 60-minute loading dose regimen".

Another key finding of CMAX CM8801 is the rate of hepatotoxicity among the subgroup of subjects who were treated within 8 hours of acetaminophen ingestion. With 95% confidence the hepatotoxicity rates could be as high as 9% for the 15-minute treatment group and as high as 12% for the 60-minute treatment group.

Hunter Area Toxicology Service (HATS)

The medical division is inclined to include the results from the Hunter Area Toxicology Service (HATS) database, an Australian observational database. The results of an observational study are rarely reported in labeling. As recommend in the draft guidance, Content and Format for the Clinical Studies Section of Labeling, the reasons for doing so should be reported.

The limitations of the study need to be presented in the label. One limitation is the quality of the database. The database primarily facilitates clinical management and, as stated in the clinical study report, no quality assurance procedures are applied to the database. Second, body weight was not recorded, so compliance with the recommended dose of 300 mg/kg I.V. acetylcysteine can not be verified. Another limitation is many

patients had multiple admissions. The analyses were limited to the first overdose treated with I.V. acetylcysteine. Subsequent admissions were not examined in the analyses of rates of hepatotoxicity. Further, the analyses were limited to only those subjects with a liver function test. Reasons leading to the need for a test were neither pre-specified nor were they reported in the clinical study report.

Finally, only one subject who did not receive treatment was reported to be at high or probable risk for hepatotoxicity. Because there was only a single subject, comparisons with those started within 8 hours can not be made.

Meta Analysis
For reasons stated in my review dated January 7, 2004, the seven articles contained in the applicant's meta-analysis do not belong in the label. Only three of the studies reported the use of I.V. acetylcysteine. Two of these used regimens different from those sought by the applicant. The third did not identify the dose and regimen used.

Adverse Reactions section
To increase readability, grid lines that are used for formatting text need to be removed from the table presenting the results from the safety study.

The rates of anaphylactoid reactions reported for the safety study need to be emphasized. This could be accomplished by adding text, moving the row to the top of the table or moving the row to a separate table that lists adverse reactions occurring at rates greater than 10%, or a combination of these.

The statement indicating comparability between the two treatments groups should be deleted.

2. Recommended labeling

Here is the labeling I propose for the Clinical Studies section.

CLINICAL STUDIES
Safety Study
A randomized, open-label, multi-center clinical study was conducted in Australia to compare the rates of anaphylactoid reactions between two rates of infusion for the I.V. acetylcysteine loading dose. One hundred nine subjects were randomized to a 15 minute infusion rate and seventy-one subjects were randomized to a 60 minute infusion rate. The loading dose was 150 mg/kg followed by a maintenance dose of 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours. {add demographic info}

Observational Study

Patients are treated according to medical guidelines in place in Australia. Thus, patients who received I.V. acetylcysteine were known to be at sufficient risk of hepatotoxicity to warrant treatment.

The recommended dose was 300 mg/kg I.V. acetylcysteine administered over 20-21 hours. However, body weight was not recorded so compliance with the recommended dose could not be assessed.

The database had information on 2246 admissions of 1749 distinct patients for treatment for acetaminophen poisoning over a 16 year period. Where a patient sought medical care for overdose more than once, only the first overdose with NAC treatment was used. Where the patient did not receive NAC treatment for any of those overdoses, only the first presentation was used. The number of admissions per patient ranged from 1 to over 10.

Of the 1749 distinct patients, 399 (23%) received I.V. acetylcysteine on at least one admission. The table summarizes the findings for this subgroup and for two other subgroups defined by Treatment other than I.V. acetylcysteine, and no treatment. Only those patients who were at high or probable risk for hepatotoxicity and who had a liver function test are included in the first row. A large proportion (60%) of subjects treated with I.V. acetylcysteine within the first 8 hours also received activated charcoal; the length of treatment for 21% was unknown.

Table. Characteristics of 1749 distinct patients who sought medical care for acetaminophen overdose.

	Time from ingestion of acetaminophen to start of I.V. acetylcysteine 399 (22%)			Treatment other than I.V. acetylcysteine 832 (48%)			No treatment 518 (30%)		
	≤8 hours n=167	> 8 hours n=210	Time unknown n=22	≤8 hours n=753	> 8 hours n=44	Time unknown n=35	≤8 hours n=352	> 8 hours n=118	Time unknown n=48
# (%) with hepatotoxicity[1] among those at high or probable risk for hepatotoxicity[2]	2 of 53 (6%)	7 of 55 (13%)	-	0 of 2 (0%)			1 of 1 (100%)		
% treated with charcoal	60%	21%	27%	85%			0%		
% whose total dose is unknown	22%	19%	27%	*			NA		
Unknown duration of treatment	21%	19%	23%	*			NA		
% at high or probable risk for hepatotoxicity[2]	71%	41%	–[3]	1%			3%		
% (n) with a liver function test	38% (64)	61% (128)	73% (16)	8.4% (70)			14% (72)		

[1] AST or ALT > 1000 U/L
[2] High or probable risk of hepatotoxicity is defined by APAP level above 150 mg/L at the four hours line, according to the Australian nomogram
[3] APAP level missing for all patients
* Values need to be added

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/s/

Lisa A. Kammerman
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FOOD AND DRUG ADMINISTRATION
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Clinical Team:	Medical reviewer: Robert Prizont, M.D.
Project Manager:	Paul Levine, Jr.

Keywords: Clinical studies, meta-analysis, historical data, observational data

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The submission does not provide substantial evidence of safety and efficacy for N-acetylcysteine injection (IV NAC).

The applicant submitted only one prospectively randomized study with a concurrent comparator arm. Moreover, it is the only study that contains the dose regimen of interest. The study compared two rates of infusion for the loading dose (15 minutes versus 60 minutes).

Although the study was planned for 500 patients, the study stopped after 180 patients were enrolled. Because of slow enrollment and the low probability of showing a difference between treatments arms if the study continued to completion, the investigators stopped the study.

The observed rate of anaphylactoid reactions among the 180 patients was 17%. This result highlights the potential safety issue with IV NAC.

If the study had been able to show a difference between the two IV NAC treatment groups in patient outcomes and in adverse reactions, the study may have provided sufficient evidence of efficacy. However, given the safety concerns with IV NAC and the lack of statistical differences between the treatment arms, this study does not provide sufficient evidence establishing the safety and efficacy of IV NAC.

The HATS database and the journal articles used in the applicant's meta-analysis to evaluate the efficacy of the IV formulation do not satisfy the standards for approval.

1.2 Brief Overview of Clinical Studies

NAC is approved in the United States as an oral formulation, but not as a solution for IV administration. The applicant is seeking approval for 300 mg/kg of an IV formulation administered for 20 hours (a loading dose of 150 mg/kg over 15 minutes followed by a dose of 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours). This regimen is approved in Europe and Canada.

The applicant submitted three reports: (1) Meta-analysis of the literature, (2) CMAX CM8801 Final Study Report and (3) HATS Analysis & Report.

CMAX CM8810 was the only study that contained the regimen being sought by the applicant, and the only randomized study comparing the regimen of interest with a concurrent comparator arm.

1.3 Statistical Issues and Findings

Meta-analysis: The results from the applicant's meta-analysis cannot be used as the basis for

a regulatory decision. The applicant's analysis pools data across studies and reports outcomes as a percentage of the number of total subjects across the studies. The analyses ignore the effect of individual studies. Nor does the submission discuss the influence of differences in study design, treatment regimens, ascertainment of cases and study populations on the outcome of their analysis.

Three studies in the meta-analysis reported the use of IV NAC. Of these, two used regimens that differ from what the applicant seeks. The other did not identify the dose and regimen used.

The Hunter Area Toxicology Service (HATS) Database for Safety and Efficacy of Intravenous N-Acetylcysteine (CMAX Report No. CM6603) is not useful either. Of 1749 patients treated for poisoning, 399 received NAC treatment. Analyses of hepatotoxicity were limited to the 20% of the patients who had liver function tests, a potential source of bias. A higher percentage receiving NAC treatment had liver function tests compared with those who did not have NAC treatment: . Of the 167 patients who received NAC treatment within 8 hours of ingestion of acetaminophen, 38.3% had a liver function test. This compares with 8.4% who were treated without NAC and 13.9% who received no treatment.

The N-Acetylcysteine Infusion Rate Study (CMAX Study No. CM8801) was the only prospectively designed randomized trial involving the dose and regimen sought by the applicant. The investigators hoped to show a lower rate of anaphylactoid reactions among those receiving a slower rate of infusion for the loading dose (IV NAC at 150 mg/kg over 60 minutes, followed by 50 mg/kg over 4 hours, and then 100 mg/kg over 16 hours) as compared with a faster rate of infusion (IV NAC at 150 mg/kg over 15 minutes, followed by 50 mg/kg over 4 hours, and then 100 mg/kg over 16 hours). Of interest, the applicant seeks approval for the faster rate of infusion.

The study was stopped after 180 patients because of slow enrollment and, if the study continued to completion, a low probability the study would show differences in rates of anaphylactoid reactions among the treatment groups. The targeted sample size was 500 patients. The incidence of anaphylactoid reactions among the 180 patients was 17%; 18% for 15-minute and 14% for 60-minute.

2. Introduction

NAC is approved in the United States as an oral formulation, but not as a solution for IV administration. The applicant is seeking approval for 300 mg/kg of an IV formulation administered for 20 hours (a loading dose of 150 mg/kg over 15 minutes followed by a dose of 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours). This dosage is approved in Europe and Canada. The decision to administer IV NAC is based on the acetaminophen level at four hours following ingestion.

This submission is the applicant's complete response to the medical division's action letter dated 30 December 2002. The original application, received 7/1/02, was given a "not approvable" because of deficiencies which included "a lack of substantial evidence from

adequate and well-controlled trials" and concerns for the potential of severe anaphylactoid adverse events.

The applicant was advised to conduct randomized, controlled trials using orally administered acetylcysteine as the active control. A meta-analysis of the literature that compares the safety and efficacy of the IV and oral routes was suggested as an alternate approach. A study report for CMAX Study No. CM8801 was also requested.

Dr. Thomas Permutt (HFD-715) reviewed the original submission and concluded there was "a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the recommended conditions of use." He also concluded there was not enough safety data.

This new submission does not persuade me to conclude otherwise regarding efficacy and safety

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Meta-Analysis of the Literature Comparing the Safety and Efficacy of Acetylcysteine Administered by the Intravenous and Oral Routes

The results from the applicant's meta-analysis cannot be used as the basis for a regulatory decision. The analyses ignore the effect of individual studies. Instead, the applicant's analysis pools data across studies and reports outcomes as a percentage of the number of total subjects across the studies. Moreover, the submission does not address the influence of differences in study design, ascertainment of cases and comparability of study populations on the outcome of their analysis.

Two literature searches identified the references. Each search used the terms "acetylcysteine" and "acute toxicity":

1. References through June 2002: An acetaminophen database maintained at Rocky Mountain Poison and Drug Center (RMPDC).
2. References through January 2003: Medline and Embase.

The searches excluded review articles, letters and reports that did not contain safety or efficacy information. "Efficacy data" means the reference reported:

1. route of NAC administration
2. time from acetaminophen ingestion to NAC treatment
3. ALT or AST values are reported
4. APAP level that is above the treatment line on the treatment nomogram (APAP level of at least 150 μg/mL at the four-hour treatment line).

The initial screening identified four hundred fifty-six (456) references published in the English language. Of these 138 contained data. All 138 contained safety information and 60 contained efficacy data.

The applicant grouped the literature into three categories:

1. Case Reports: (81 references)
   97 subjects with safety data
   30 with efficacy data
2. Reports of studies with data at the patient level: (13 references)
   174 subjects with safety data
   97 with efficacy data
3. Reports of studies with data grouped by treatment: (44 references)
   10,547 with safety data
   2808 with efficacy data

Table 1: Disposition of references

	# of articles	Efficacy and Safety	Safety only
Type of published reference			
Case reports	81	30 patients*	67 patients*
Clinical studies (All)	57	15 articles	42 articles
Individual Patients	13	8 articles	5 articles
Aggregated by Treatment group	44	7 articles	37 articles

* Case reports describe individual patients. Some published articles describe more than one case report.

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Table 2. Disposition of subjects by type of references

	# patients	Efficacy	Safety
Type of published reference			
Case reports	97 patients	30 patients	97 patients
Clinical studies (All)			
Individual Patients	174	97	174
Aggregated by Treatment group	10547	2808	10547

Source: Section 9.1 of study report

Study Objectives

The study objectives were both the efficacy and safety of IV NAC treatment:

Efficacy:

IV NAC versus oral NAC in all treatments
Early IV NAC treatment compared to early oral NAC treatment
Late IV NAC treatment compared to late oral NAC treatment
Early NAC treatment compared to late NAC treatment
Early IV NAC treatment compared to late IV NAC treatment
Early oral NAC treatment compared to late oral NAC treatment

Safety

To evaluate the safety profile of IV NAC and oral NAC treatment as measured by adverse events, mortality, and anaphylactoid reactions.
To evaluate the effects of IV NAC and oral NAC on renal function as measured by a change from baseline in serum creatinine using the highest serum creatinine reported at least 24 hours after baseline.

Design

Analyses were conducted for each of the following groups of literature:

Case reports, Safety (all case reports)
Case reports, Safety (all clinical studies)
Clinical studies, Safety (all clinical studies)
Clinical studies, Efficacy (studies that meet eligibility criteria)
Clinical studies, Other (qualitative review of studies that do not meet efficacy criteria)

Efficacy Results

Because the literature that reports results by treatment group accounts for over 10,000 patients while those reporting case reports and results at the patient level together account for fewer than 300 patients, **my review focuses only on the results aggregated by treatment group.**

Aggregation by Treatment Group:

The applicant identified seven references in which patients were classified by treatment group. These references, according to the applicant, provide efficacy data on 2808 patients. The references together with characteristics unique to each reference are:

Table 3

Reference	Study Design, Study Dates	Route, NAC Dose, Regimen	Study Population	Notes
Bond (1999)	***Retrospective chart review*** 1991 - 1995 Two hospitals exclusively serving a four-county population (Virginia) Study objective: estimate the incidence of ER evaluations of acute acetaminophen ingestion, incidence of hospitalizations	**Not described**	>10 years of age	636 charts reviewed 122 presented after acute, single-dose ingestion of acetaminophen overdose 25 of 122 hospitalized *18 presented within 18 hours*; *7 presented greater than 18 hours*;
Buckley (1999)	***Post-hoc analysis of a prospectively defined case series*** 1987 - 1996 Australia Note: The applicant's analysis includes only those data from Buckley's study of IV NAC, which I agree is appropriate. The meta-analysis reported by Buckley includes three studies [Smilkstein (1991), Rumack (1981) and Smilkstein (1988)] contained in the applicant's meta-analyis.	**IV** 300 mg/kg IV over 20 hours. Loading dose for an unspecified number of patients is over 15 minutes; for other patients it's between 15 minutes and one hour	Patients admitted with suspected or confirmed acetaminophen poisoning	Of 205 treated with NAC, *86 in probable and high risk groups* Age: Median=24 years, range: 0 to 89. 64% female.
Prescott (1981)	***Unknown***; ascertainment of IV-treated subjects is not described. Start date unknown, but probably after 1973 (when cysteamine was introduced). Stop date assumed <1981 (date of publication) Controls: Supportive therapy: 57 patients admitted prior to 1973. IV cysteamine or methionine: 60 patients Edinburgh, Scotland	**IV** Dose and administration not described	Adults with APAP overdose	*100 subjects* M/F: 42/58 Age: 33 (13 to 82)

Rumack (1981)	***Prospective, open label, single arm study, multi-clinic.*** First 662 subjects, starting in 1976 Rocky Mountain Poison Center, Denver	Gastric aspiration and lavage without activated charcoal or administration of cathartics. If charcoal had been given, the stomach was relavaged until clear. **Oral** over 72 hours. Diluted with soda pop or grapefruit juice. LD: 140 mg/kg MD: 70 mg/kg orally q4h for 17 additional doses If patient vomited a loading or maintenance dose within one hour, the dose was repeated.	High risk Age ≥12 years History of known or suspected acute ingestion of 7.5 g or more of acetaminophen within 24 hours of admission	*155 subjects treated, probable risk and late probable risk* Liver function tests were standardized to allow comparisons among sites.
Smilkstein (1991)	***Prospective, multicenter study*** 1984 - 1990 Rocky Mountain Poison Center, Denver	**IV (48 hour protocol)** LD: 140 mg/kg IV over 60 minutes MDD: 12 doses of 70 mg/kg IV every 4 hours	Young adults and children presenting with a single acute acetaminophen overdose. Initiation of IV NAC within 24 hours of ingestion. Treatment with at least 12 doses of IV NAC	*179 patients* M/F 32.4%/67.6% Age: mean=21 55.9% between 10 and 20 3.4% (n=6) lt 5 yo 41.3% high risk 75.4% probable 24.6% possible risk

Smilkstein (1988)	***Prospective, multicenter study*** 1976 to 1985 Rocky Mountain Poison Center, Denver	**Oral** LD: 140 mg/kg MD: q4hrs, 70 mg/kg for 17 doses	Young adults and children presenting with a single acute acetaminophen overdose. Analyses limited to patients who had at least 17 doses of NAC given per protocol.	*2540 patients*. Of these 2023 had acetaminophen values above the study nomogram line, and were included in the analyses. M/F 30.8%/69.2% Age: 78.3% between 10 and 30 years of age 3.3% of all patients and 1.4% of those at high risk for hepatotoxicity were under five years old
Riggs (1989)	***Prospective study*** 1976 to 1985 Rocky Mountain Poison Center, Denver Likely a subset of Smilkstein (1988) Objective: pregnancy outcomes	**Oral**		113 patients reported to be pregnant at time of overdose 24 had toxic acetaminophen levels. 20 treated within 16 hrs; 4 gt 16 hrs.

Five of the above studies, including all studies reporting on IV NAC, are not relevant to establishing the efficacy of IV NAC.

1. Pregnancy outcomes among pregnant women, who ingested an overdose of acetaminophen, are the focus of Riggs (1989); little other data are presented. Moreover, Riggs (1989) is likely a subset of Smilkstein (1988). **Oral NAC** was the subject of both.
2. The objective of Bond (1999) is to estimate incidence rates of acetaminophen related emergency room evaluations and hospitalizations. **The route and administration of NAC is not described.**
3. Prescott (1981) does not describe the ascertainment of subjects or the dates of ascertainment. Presumably, patients were treated between 1973 and 1981. **The dose and regimen of IV NAC is not described.**
4. Buckley (1999) **uses an IV NAC treatment regimen that may differ from the one proposed by the applicant.** They recommend administration of activated charcoal with IV NAC. Although I could not find this regimen described in the article, it is likely active charcoal was administered because their usual management of subjects presenting within 4 hours who have taken >125 mg/kg of acetaminophen is to administer activated charcoal and IV fluids. Presumably, if the four-hour acetaminophen level was sufficiently high, then they would be given IV NAC.

   Please note the applicant's analysis includes only those data from Buckley's study of IV NAC, which I agree is appropriate. The meta-analysis reported by Buckley includes three studies [Smilkstein (1991), Rumack (1981) and Smilkstein (1988)] contained in the applicant's meta-analyis; see Table above.
5. Smilkstein (1991) **uses an IV NAC regimen that differs from the one proposed by the applicant**: LD: 140 mg/kg IV over 60 minutes, followed by 12 doses of 70 mg/kg IV every 4 hours. The entire dose was administered over 48 hours, compared with the 20 hours proposed by the applicant. Smilkstein (1991) note limitations of the study, including the lack of randomization of subjects to treatments. Ethanol use and liver disease were categorized as absent or present according to a patient's history. Data for other potentially important variables were not collected. Data were limited to patients who received the entire course of IV NAC.

The remaining two studies, Smilkstein (1988) and Rumack (1981) report on **oral NAC.**

3.1.2 Analysis of the Hunter Area Toxicology Service (HATS) Database for Safety and Efficacy of Intravenous N-Acetylcysteine (CMAX Report No. CM6603)

The objective of this study was to evaluate the safety of NAC IV for the treatment of overdose of acetaminophen using the Hunter Area Toxicology Service (HATS) database. HATS prospectively collects data on poisonings in patients who present to the hospitals in the greater Newcastle area in New South Wales, Australia.

The purpose of the database is primarily for facilitating clinical management, not for analysis of a clinical trial. Moreover, the types of data collected over time have changed. No quality

assurance procedures are applied.

Patients are treated according to medical guidelines in place in Australia. According to the medical practice guideline, patients in the database who did not receive IV NAC treatment should not have been treated. Thus, patients who received IV NAC were known to be at sufficient risk of hepatotoxicity to warrant treatment with IV NAC. The APAP cases included in this report span a 16 year period, from 16 Jan 1987 to 10 Jan 2003.

All analyses were retrospective and exploratory. Prospective hypothesis testing was not planned. Primary endpoints included incidence of adverse drug reactions, mortality, renal function and Glasgow Coma Scales. The secondary objective was to assess the efficacy of NAC administered IV for the treatment of overdose of acetaminophen. Endpoints were liver function tests (AST, ALT).

Two datasets were created: by patient (each patient appears only once) and by admission (all cases of overdose). My comments focus on the "by patient" analyses.

The database provides information on 2246 admissions of 1749 distinct patients for treatment for poisoning after ingestion of acetaminophen. Of these, 399 patients received treatment with NAC on at least one admission (22.8%) while 1350 patients were not administered NAC (77.2%). Of the 1350 patients who did not receive NAC on at least one admission, 832 received some other treatment following ingestion of acetaminophen; the other 518 patients did not receive any treatment on their first admission.

Of the 399 patients who received NAC treatment 204 (51.1%) received NAC treatment according to the standard treatment protocol regimen with duration of treatment between 20 and 21 hours. The recommended dose is 300 mg/kg administered over 20-21 hours. Body weight was not recorded in the database.

Patients ranged in age from 2 months to 96 years. The youngest patient who was treated with NAC was 4 years old and the oldest was 96 years. 71.4% of patients were 16-40 years.

Of the patients who received NAC treatment, 137 (34.3%) had ingested only acetaminophen while 266 had also ingested toxins other than acetaminophen. The proportion (24%) that ingested co-poisons of major toxic importance was similar to the proportion (22.4%) that received treatment but not NAC.

Of the 399 patients who received NAC treatment, 151 (37.8%) also received treatment with charcoal. Within 8 hours of ingestion of APAP, 101 of 167 patients received activated charcoal.

Liver function was assessed using AST and ALTs. **The authors of the study report conclude IV NAC reduces hepatotoxicity** as demonstrated in comparisons with those treated with IV NAC within 8 hours of acetaminophen ingestion versus greater than 8 hours of acetaminophen ingestion, and **in a comparison of those treated with IV NAC within 8 hours of acetaminophen ingestion versus those not treated.**

These results, however, are not interpretable because the analyses are limited only to those with liver function tests. Overall, only 20% had a liver function test. Of those who received NAC treatment within 8 hours of ingestion of acetaminophen, 38.3% of patients had a liver function test. This compares with 8.4% who were treated without NAC and 13.9% who received no treatment. It is very **likely the rate of hepatotoxicity is overestimated in those not receiving NAC treatment.** A patient's clinical condition may have triggered LFTs.

Liver Function Tests (ALT or AST)	Ingestion of APAP to NAC Treatment						Treatment, No NAC		No Treatment		Total	
	<= 8 hours		> 8 hours		Unknown							
	N	% of Group	N	% of Group	N	% of Group	N	% of Group	N	% of Group	N	% of Group
ALT &/or AST	64	38.3%	128	61.0%	16	72.7%	70	8.4%	72	13.9%	350	20.0%
ALT & AST	10	6.0%	58	27.6%	9	40.9%	23	2.8%	17	3.3%	117	6.7%
AST only	4	2.4%	7	3.3%	2	9.1%	13	1.6%	8	1.5%	34	1.9%
ALT only	50	29.9%	63	30.0%	5	22.7%	24	4.1%	47	9.1%	199	11.4%
No ALT or AST	103	61.7%	82	39.0%	6	27.3%	762	91.6%	446	86.1%	1399	80.0%
Group Total (% of Total)	167	9.5%	210	12.0%	22	1.3%	832	47.6%	518	29.6%	1749	100.0%

Source: Table 10.4.1 of Study Report

3.1.3 Analysis of "N-Acetylcysteine Infusion Rate Study"; CMAX Study No. CM8801

The study objective was to determine if the incidence of adverse events (AEs) due to intravenous NAC is significantly less for a 60-minute infusion rate for the initial dose compared with the standard infusion of the initial dose over 15 minutes. A secondary objective was to assess the efficacy of the two treatment arms. An additional analysis included an investigation of differences in efficacy between 15-minute and 60-minute infusion times for early and late treatment (NAC treatment within 8 hours of acetaminophen ingestion and more than 8 hours after ingestion, respectively).

The two treatment groups are:

1. IV NAC at 150mg/kg over 60 minutes, followed by 50 mg/kg over 4 hours, and then 100 mg/kg over 16 hours
2. IV NAC at 150 mg/kg over 15 minutes, followed by 50 mg/kg over 4 hours, and then 100 mg/kg over 16 hours

The study was a randomized, prospective trial conducted at seven study sites in Australia. The randomization was not done in blocks and study medication was not blinded. The study was powered to detect a reduction of 10% in anaphylactoid reactions. Although the target sample size was 500 patients, the investigators terminated the study after 180 evaluable patients were enrolled.

They cited difficulty in obtaining data on the 500 patients in a reasonable period and, based on the observed data, the study was unlikely to show clinical and statistically significant differences between the two regimens for the primary endpoint (rate of anaphylactoid reactions). At the time of termination and after four years of patient enrollment, the observed difference between treatments in the rate of anaphylactoid reactions was 4%:

18% (20 of 110) for the 15-minutes treatment group and 14% (10 of 70) for the 60-minute treatment group.

Patients who presented to hospitals with acetaminophen poisoning that required the administration of NAC, as determined by medical practice guidelines, were eligible to participate. One hundred eighty patients (180) were enrolled between 06 May 1999 and 12 March 2003. Of these 48 were male, 132 were female. One hundred nine patients (109) were randomized to the 15-minute treatment arm and 71 patients were randomized to the 60-minutes treatment arm. Fifty-eight patients were treated within 8 hours of acetaminophen ingestion and 112 patients were treated more than 8 hours after ingestion.

Drug related AEs were observed in 45% of the patients randomized to the 15-minute treatment arm (49 of 109 patients) and in 38% of the patients randomized to the 60-minute treatment arm (27 of 71 patients). Anaphylactoid reactions were recorded for 30 (17%) of the patients n the study; 18% for 15-minute and 14% for 60-minute.

Overall, no significant differences in maximum measured ALT existed between the 15-minute (5.6%) and 60-minute (8.7%) infusion treatment groups. ALT was used because it was measured for most patients (n=177); only 119 patients had an AST measurement.

Marked differences in maximum ALT existed between patients treated within eight hours of ingestion and those treated after eight hours, regardless of treatment group. Patients treated within eight hours of ingestion did not experience hepatotoxicity while those treated beyond eight hours had a 10% rate of hepatotoxicity. These differences appeared to persist in both the 15-minute and 60-minute infusion treatment groups.

3.2 Safety evaluation

Anaphylactoid reactions appear to be more common among patients receiving IV NAC.

4. Summary and Conclusions

4.1 Statistical Issues and Collective Evidence

Meta-analysis: The results from the applicant's meta-analysis cannot be used as the basis for a regulatory decision. The analyses ignore the effect of individual studies. Instead, the applicant's analysis pools data across studies and reports outcomes as a percentage of the number of total subjects across the studies. The submission does not address the impact of differences in study design, ascertainment of cases and study populations on the outcome of their analysis.

Three studies reported the use of IV NAC. Of these, two used regimens that differ from what the applicant seeks. The other did not identify the dose and regimen used.

The Hunter Area Toxicology Service (HATS) Database for Safety and Efficacy of Intravenous N-Acetylcysteine (CMAX Report No. CM6603) is not useful either. Analyses of hepatotoxicity were limited to those patients who had liver function tests. Overall, only 20% had a liver function test. A higher percentage receiving NAC treatment

had liver function tests compared with those who did not have NAC treatment. Of those who received NAC treatment within 8 hours of ingestion of acetaminophen, 38.3% of patients had a liver function test. This compares with 8.4% who were treated without NAC and 13.9% who received no treatment.

The N-Acetylcysteine Infusion Rate Study (CMAX Study No. CM8801) was a prospectively designed randomized trial. The investigators hoped to show a lower rate of anaphylactoid reactions among those receiving a slower rate of infusion for the loading dose (IV NAC at 150mg/kg over 60 minutes, followed by 50 mg/kg over 4 hours, and then 100 mg/kg over 16 hours) as compared with a faster rate of infusion (IV NAC at 150 mg/kg over 15 minutes, followed by 50 mg/kg over 4 hours, and then 100 mg/kg over 16 hours).

The study was stopped after 180 patients because of slow enrollment and, if the study continued to completion, a low probability the study would show differences in rates of anaphylactoid reactions among the treatment groups. The targeted sample size was 500 patients. The incidence of anaphylactoid reactions among the 180 patients was 17%; 18% for 15-minute and 14% for 60-minute (p=.49).

4.2 Conclusions and Recommendations

The results submitted do not support the efficacy of IV NAC. CMAX Study CM8801 was the only prospectively randomized trial comparing the treatment of interest with a concurrent control. Unfortunately, because the study was stopped after 180 patients, there were not sufficient numbers of patients in the two treatment arms to allow a non-inferiority comparison of the rates of anaphylactoid reactions. The incidence of anaphylactoid reactions among the 180 patients was 17%; 18% for the 15-minute treatment group and 14% for the 60-minute treatment group.

The HATS database and the journal articles used in the applicant's meta-analysis to evaluate the efficacy of the IV formulation do not satisfy the standards for approval. The analysis of the HATS database was limited to those patients who had a liver function test. Overall 20% had a test; 38.3% of those who received NAC treatment within 8 hours of ingestion of acetaminophen had a liver function test compared with 8.4% who were treated without NAC and 13.9% who received no treatment. None of the journal articles used the dose and regimen sought by the applicant.

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-539
Name of drug:	Acetadote (acetylcysteine injection)
Applicant:	Cumberland
Indication:	antidote for acetaminophen overdose
Documents reviewed:	volumes 2, 10, 11, 13; electronic submissions at \\Cdsesub1\n21539\N_000\2002-11-04\clinstat\CM8801 Study\Report Text.pdf and \\Cdsesub1\n21539\N_000\2002-11-27\Clinstat\TabularNACEfficacy.pdf
Project manager:	Brian Strongin
Clinical reviewer:	Robert Prizont, M.D.
Dates:	Received 7/1/02; user fee (6 months) 1/1/03
Statistical reviewer:	Thomas Permutt, Ph.D. (team leader)
Biometrics division director:	S. Edward Nevius, Ph.D.

Keywords: NDA review, clinical studies, active control/noninferiority, historical control

The body of this review is short enough to serve as its own executive summary; therefore, no separate summary is provided.

1 CONCLUSIONS AND RECOMMENDATIONS

The subject NDA consists of reports of literature on the use of acetylcysteine under different conditions than those recommended, along with an interim report of a new trial comparing two dosing regimens. The new trial neither reliably shows differences between the regimens, which would be evidence of efficacy, nor reliably shows sufficient similarity to be combined with external data as evidence of efficacy. There is therefore a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the recommended conditions of use.

There are also questions of safety that do not appear adequately to have been addressed. As the drug is intended to treat a life-threatening condition, lack of efficacy is itself a safety issue, and anaphylactoid reactions are also to be expected. The CMAX study was designed to address these issues, but data on only 95 of the planned 500 patients are reported in the application. The completed study as planned would appear to be reasonably applicable to a determination of safety.

2 INTRODUCTION AND BACKGROUND

Acetylcysteine solution, 10% and 20%, is marketed under NDA 13-601 and a dozen ANDAs. It is administered by inhalation in indications unrelated to the present NDA. It is also approved for ingestion or administration by nasogastric tube as an antidote to poisoning by overdose of acetaminophen. According to the application, intravenous formulations are approved in some other countries for acetaminophen poisoning, and "NAC [N-acetylcysteine] is currently used intravenously and in a nonstandardized manner" in the United States. The intravenous route offers the putative advantages of greater tolerability (the oral solution smells bad), possibility of effective administration to a vomiting patient, and, perhaps, greater bioavailability. The question of bioavailability, however, is a complex one. The plasma concentration of oral acetylcysteine is limited by efficient metabolism in the liver, and the liver is the site of most toxicity of acetaminophen and thus presumably the site of action of acetylcysteine. Thus, it is possible that acetylcysteine is not much in the plasma after oral administration because it has already gone where it needed to go.

The subject NDA concerns a solution of acetylcysteine 20% for intravenous administration. The proposed regimen is a loading dose of 150 mg/kg in 200 mL of 5% dextrose, infused over [redacted], followed by a maintenance dose of 50 mg/kg in 500 mL of 5% dextrose infused over four hours, then 100 mg/kg in 1000 mL of 5% dextrose over 16 hours.

3 DATA ANALYZED AND SOURCES

The NDA supplies copies of about 50 publications, mostly reports of uncontrolled experience with acetylcysteine. It identifies four of these as "primary," along with an interim report of a single, ongoing study. The table below (an electronic submission) not only

summarizes these studies; it also constitutes the only integrated discussion in the application of the basis for a finding of efficacy.

Tabular Summary of Clinical Efficacy Data, Primary Studies

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
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 5 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[b]:0 M/F NK, but mostly F Age: 21(9.5)	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.
Oh (1900)	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: 57 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. CM8801	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	96:0 (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 83)	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

The Keays study was a randomized, controlled experiment, but in a different clinical condition (fulminant hepatic failure) than the proposed indication. The "efficacy results" of

the other studies from the literature appear to be fairly summarized, which is to say, there are no results of the complete, quantitative, comparative kind that would be taken as substantial evidence of efficacy according to the usual standards of review. Furthermore, all these studies used different regimens than that recommended in the proposed labeling. The new (CMAX) study, however, compares a regimen similar to that in some other studies to the proposed regimen. It will be reviewed in some detail, with a view to answering two questions. First, does it provide in itself evidence of the efficacy of the proposed regimen? Second, to what extent does it indicate noninferiority to another regimen, which, combined with evidence of efficacy of the other regimen, might be taken as evidence of efficacy of the proposed regimen?

4 CMAX STUDY

Besides the literature reports, the clinical data in the application consist of an interim report of a single randomized study. The study is described in the application as "supported by" the applicant, and the study report lists "Cumberland Pharmaceuticals Inc" as "sponsor," but in a telephone conversation 19 December 2002, representatives of the applicant said it was not sponsored by them. " (CMAX)," possibly a organization, with address in the , is listed as "external monitor." ' was principal investigator. The study is being carried out at six hospitals in Australia. Five hundred patients were to be studied, but the interim report includes data on only 96 patients. Cumberland had discussed with the Agency the submission of an application based on literature only, and the Agency had advised that at least an interim report of the CMAX study should also be included.

The study compared two dosage regimens of the test article: one (which I shall call the slow regimen) corresponding to the , and the other in which the loading dose was infused over 15 minutes (fast) instead of 60 minutes. The primary objective was apparently to determine if the slower infusion would reduce the risk of adverse events, particularly anaphylactoid reactions. According to the report, "A secondary objective of the study was to assess the efficacy of the two treatments. The secondary endpoints used in the assessment of this objective were liver function tests (AST, ALT, INR)." Rather than a formal demonstration either of superior or of equivalent efficacy, the purpose seems to have been a general conclusion that the slower regimen, if it were safer, was not also notably less effective.

4.1 RANDOMIZATION

Patients were allocated centrally to the two groups by an old-fashioned method. Five hundred slips of paper, 250 for each regimen, were put in a box, and when a patient was enrolled, a slip was drawn. Of the 96 patients discussed in the interim report, 61 were assigned to the slower infusion.

This imbalance may seem more remarkable than it is. If the study had proceeded to conclusion, there would have been no imbalance because all the slips would have been used. Most studies are randomized in blocks so that wide imbalances are impossible even in

interim analysis, whereas this study used a method that did not guarantee interim balance. Still, even under the actual conditions, an imbalance this big would happen only about once in 100 times. It seems likely that the slips were not well mixed in the box.

Even so, I do not think the interpretation of the results should be much affected. It is of little consequence that different numbers of patients were randomized to the two treatments. There is no reason to think that the difference or similarity in outcomes between the two groups, which is what matters, should be systematically related to the size of the groups.

4.2 SAFETY RESULTS

The interim report summarizes the safety results as follows:

> Eighty percent (80%) of patients randomized to the 15-min treatment arm and 63% of patients randomized to the 60-min treatment arm experienced an adverse event following initial NAC administration. Drug-related AEs, the primary endpoint, were observed in 56% of the patients randomized to the 15-min treatment arm (34 of 61 patients) and 43% of the patients randomized to the 60-min treatment arm (15 of 35 patients). The difference between the incidence of drug-related AEs is not statistically significant (the difference is 13%, with a standard error of 11%, p = 0.22). Drug-related AEs occurring within two hours of initiation of treatment were observed in 46% of the patients randomized to the 15-min treatment arm (28 of 61 patients) and 40% of the patients randomized to the 60-min treatment arm (14 of 35 patients). The difference between the incidence of drug-related AEs occurring within two hours of initiation of NAC treatment is not statistically significant (the difference is 6%, with a standard error of 10%, p = 0.57). The predominant drug-related adverse event experienced by patients within two hours of initiation of NAC was an anaphylactoid reaction. The observed rates of anaphylactoid reactions for the two treatment groups were 23% (14 of 61 patients) for the 15-min initial NAC infusion and 20% (7 of 35 patients) for the 60-min initial NAC infusion. There was one patient in each group who experienced a severe anaphylactoid reaction. With the small number of patients involved in the study, the difference between the rates of anaphylactoid reactions in the two groups is not statistically significant (the difference is 3%, with a standard error of 9%, p = 0.74). There were no deaths or serious AEs reported.

From these nonsignificant differences the applicant concludes, "The overall safety profile of the 60-minute loading dose compared to the 15-minute loading dose appears preferable."

4.3 APPLICANT'S EFFICACY RESULTS

Two of the three planned liver function tests, AST and INR, are missing in a quarter to half the patients. Only ALT was measured in nearly all patients randomized. The results are summarized in the table below (from volume 1.2 by our numbering, but labeled "volume 13., p. 64).

Table 4 **Maximum Measured ALT, AST, and INR Results: CMAX Study No. CM8801**

Parameter/Range	60-Minute Loading Dose Regimen (N=34) n (%)	15-Minute Loading Dose Regimen (N=61) n (%)
ALT		
Normal (0-55)	22 (65)	48 (79)
Elevated (56-150)	3 (9)	7 (11)
Lesser hepatic injury (151-1000)	5 (15)	3 (5)
Hepatotoxicity (>1000)	4 (12)	3 (5)
Unknown	1 (3)	0 (0)
AST		
Normal (0-45)	12 (35)	29 (48)
Elevated (46-150)	2 (6)	4 (7)
Lesser hepatic injury (151-1000)	1 (3)	2 (3)
Hepatotoxicity (>1000)	2 (6)	3 (5)
Unknown	18 (51)	23 (38)
INR		
Normal (0-1.2)	14 (56)	27 (57)
High (>1.2)	11 (44)	20 (43)
Unknown	10 (29)	14 (23)

Source: CMAX Study No. CM8801, Appendix 10.3.1

A two-sided p-value of 0.18 is reported for a rank-sum test on the ALT values. The rates for hepatotoxicity against the other categories combined were also found to be not statistically significantly different, although the incidence of hepatotoxicity in the slower group (12 percent) was more than twice that in the faster group (5 percent).

The interim report points out that all seven cases of hepatotoxicity occurred in patients who began therapy with acetylcysteine more than eight hours after their overdose of acetaminophen. Thus, in the subgroup treated before eight hours, the rates were zero in both groups. The report argues that this may be the most relevant comparison:

> Previous studies have shown that hepatotoxicity is rare in patients who receive NAC treatment within 8 hours of paracetamol [acetaminophen] exposure (Smilkstein, Knapp, et al. 1988). Once 8 hours has elapsed in patients with at risk paracetamol concentrations, sufficient NAPQI [a toxic metabolite of acetaminophen] 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.

From the nonsignificant though numerically substantial difference in hepatotoxicity, as well as the fact that it is all attributable to differences beyond eight hours, the sponsor concludes that the efficacy was not different between the two regimens. Accordingly, the proposed labeling recommends the slower, putatively safer, regimen.

4.4 REVIEWER'S ADDITIONAL EFFICACY ANALYSES

I do not agree that the data past eight hours should be ignored. Indeed, I think they are the nearest thing in the application to evidence of efficacy. There is information, first, in the

comparison of the two regimens in patients who were not treated in the first eight hours and, second, in the comparison between these patients and those who were treated promptly.

Sixty-six of the 95 patients studied, more than two thirds, received acetylcysteine more than eight hours after taking acetaminophen. Of these, 43 were in the fast group and 23 were in the slow group. The rate of hepatotoxicity in the fast group was 7 percent (3/43), and in the slow group it was 17 percent (4/23). The difference is not statistically significant ($p = 0.22$, Fisher's exact test), but it is at least as suggestive as any of the other, nonsignificant results presented. If there is differential efficacy between the two regimens, even past eight hours, it needs to be weighed against the putative differential risk. In clinical practice as well as in the study, it may happen that many patients are not treated for more than eight hours after taking acetaminophen. I do not mean to dispute the conclusion that, on balance, the slower regimen might be better, at least for patients treated promptly, but only to question the way the conclusion appears to have been reached.

For the present purpose, however, differential efficacy would have another, important implication. If the regimens are differently effective, then at least one of them *is* effective, unless one or both are harmful. Reliable evidence of a difference between the regimens would also be evidence of the effectiveness of acetylcysteine, which is necessary for approval and is not manifest elsewhere in the application. This nonsignificant difference does not constitute such reliable evidence, but similar findings in a larger study, such as the present study continued to completion, might be a part of such evidence.

The comparison between patients treated before and after eight hours likewise could furnish some evidence of efficacy. A natural experiment has occurred, with some patients receiving acetylcysteine promptly and others unfortunately not. The fact that hepatotoxicity occurs in some of those not treated promptly gives meaning to the observation that it has not occurred in those treated promptly, regardless of regimen. Ignoring the regimen, 7 of 66 (11%) of late-treated patients suffered hepatotoxicity, compared to 0 of 29 early-treated patients. Again, this difference is not statistically significant. (The p-value is 0.1 for Fisher's exact test, pooling the two regimens. It would probably be more appropriate to stratify by regimen, but the usual tests based on chi-square or logistic regression would be unreliable given the small cell counts.) Again, however, it seems more meaningful to me than some other, nonsignificant results that are presented.

4.5 NONINFERIORITY

The CMAX study, I have concluded above, does not in itself provide substantial evidence of efficacy of acetylcysteine. There are apparent differences, between treatment regimens and between early- and late-treated patients, that are suggestive of efficacy, but they are not statistically reliable. If these differences are not large enough to be significant, are they small enough to show noninferiority? That is, taken together with evidence from other studies of the efficacy of the comparator regimen, might they provide indirect evidence of the efficacy of the proposed regimen?

I do not think so. The interim report concludes that there are unreliable but potentially meaningful differences in safety between the regimens. It minimizes comparably unreliable but potentially meaningful differences in efficacy, arguing that the most relevant efficacy data are those on 29 patients treated within eight hours. In any case, it can hardly be argued that the data from these 29 patients rule out a meaningful difference between the regimens. The only reasonable conclusion is that the data are too limited reliably to show such a difference.

Furthermore, the data from other studies, at least as they are presented in the application, are not of the kind that could be combined with a finding of noninferiority to constitute evidence of efficacy of the new regimen. At best, the literature reports could be taken as indicating that the comparator regime has some effect in some populations. What would be needed would be evidence of how much the effect was and how reliably it could be measured in a population similar to the one in the CMAX study. Such historical evidence of sensitivity to drug effects might then allow the establishment of a margin of noninferiority for the CMAX study. Such historical evidence of sensitivity is lacking here, and so also is the basis for a margin. Besides, it hardly seems possible that an appropriate margin could be large enough to encompass the huge range of uncertainty in the interim CMAX data.

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Thomas Permutt
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S. Edward Nevius
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