CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-539

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-539
Brand Name:	Acetadote
Generic Name:	Acetylcysteine
Dosage form and Strength:	Sterile Injection Solution (20%; 10 and 30 ml vials)
Route of administration:	Intravenous (IV)
Indication:	[redacted]
Sponsor:	Cumberland Pharmaceuticals
Type of submission:	Original NDA
Clinical Division:	HFD-180
OCPB Division:	HFD-870/DPE II
Priority:	Priority
Submission date:	07/01/02 (N-000), 10/15/02 (BZ)
OCPB Consult date:	07/05/02
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Suresh Doddapaneni, Ph.D.

I. Executive Summary

Currently, Mucomyst (acetylcysteine oral 10 and 20%) is approved as an oral antidote to prevent or lessen hepatic injury, which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. Under NDA 21-539, Cumberland Pharmaceuticals is seeking approval of Acetadote Injection (Acetylcysteine, 200 mg/ml or 20%) for intravenous (IV) treatment [redacted]acetaminophen overdose. The proposed IV dosing regimen is as follows (without initial induction of emesis):

Loading dose: 150 mg/kg in 200 ml of 5% dextrose, IV infusion ove[redacted],
Maintenance dose: 50 mg/kg in 500 ml of 5% dextrose, IV infusion over 4hrs followed by 100 mg/kg in 1000 ml of 5% dextrose over 16 hrs.

In support, 14 literature articles were submitted describing the general pharmacokinetics (PK) of acetylcysteine. PK data in healthy volunteers/patients after IV administration of a similar regimen (the same loading dose but with a shorter duration of 15 minutes) was available. However, no formal PK studies were conducted to support the proposed IV dosing regimen. In order to extrapolate oral Mucomyst's safety/efficacy data to Acetadote IV use, simulations attempted to link the acetylcysteine plasma profiles after oral dosing of Mucomyst (with a

reported oral bioavailability of around 10%) and those after IV dosing of Acetadote were not successful.

A. Recommendations

NDA 21-539 for Acetadote Injection is acceptable from the viewpoint of OCPB/DPEII provided a satisfactory agreement can be reached with respect to the language in the package insert (PI). The recommended labeling changes (page 8) should be conveyed to the sponsor.

General Comment: (To Clinical Division)

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11/08/02
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Suresh Doddapaneni, Ph.D. 11/19/02

FT initialed by Suresh Doddapaneni, Ph.D. 11/21/02

cc: NDA 21-539, HFD-180 (R. Prizont, H. Gallo-Torres, B. Strongin), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski).

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Under the Human PK/Bioavailability Section (Item 6) of NDA 21-539, 14 literature articles were submitted. In these articles, different formulations such as effervescent tablet, slow-release tablet, fast dissolving tablet, and granulate dosage forms were used for oral dosing and Parvolex® (currently approved outside the US) and/or aqueous solutions of acetylcysteine were used for IV dosing.

No raw data, assay method (and validations), or acetylcysteine plasma profiles of Mucomyst after oral dosing was provided along with the literature articles. Comparative PK data for oral dosing of Mucomyst and IV dosing of Acetadote is not available.

The proposed Acetadote IV dosing regimen is quite different from the currently approved oral dosing regimen of Mucomyst. Upon HFD-180's requests, simulations were undertaken in an attempt to extrapolate oral safety/efficacy data for IV use, i.e., to link the acetylcysteine plasma profiles after oral dosing of Mucomyst (with a reported oral bioavailability of around 10%) and those after IV dosing of Acetadote based on literature information. Due to limited information available, it rendered the above attempt unsuccessful.

One pivotal clinical trial (No. **CM8801**) was conducted in 96 patients to support the proposed Acetadote IV dosing and it is mainly for safety endpoint evaluation. Only 35 patients were under the proposed IV dosing group and the rest of 61 patients were under another IV dosing group using the currently approved IV treatment outside the US (e.g., UK, German, Australia, and New Zealand) with a slightly different loading dose infusion time (15 min), i.e.,

Loading dose:	150 mg/kg in 200 ml of 5% dextrose, IV infusion over 15 min,
Maintenance dose:	50 mg/kg in 500 ml of 5% dextrose, IV infusion over 4hrs followed by 100 mg/kg in 1000 ml of 5% dextrose over 16 hrs.

Acetaminophen plasma levels from most of the patients admitted to the hospital and during the treatment were also obtained. Efficacy, however, was assessed only in a subset of patients who received acetylcysteine IV treatments within 8 hr post ingestion of acetaminophen, 10 patients (10/34 with one dropout) who received acetylcysteine IV treatment (60-min loading) and 18 patients (18/61) from the comparative group receiving acetylcysteine IV treatment (15-min loading).

No reported significant difference was found in terms of hepatotoxicity between two IV treatments when given at the time of < 8 hr post ingestion of acetaminophen. The overall rate of hepatotoxicity between two IV treatment groups was also reported NOT significantly different, 12% (4/34) for the 60-min loading group and 5% (3/61) for the 15-min loading group (p=0.22).

IV. Question Based Review

A. General Attributes

Mucomyst (acetylcysteine oral 10 and 20%) was approved prior to 01/01/82 as a mucolytic agent (NDA 13-601). Little or no PK information was included in Mucomyst's NDA. Subsequently, it was approved (under a clinical supplement) as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen (generally, 150 mg/kg or more). Generic acetylcysteine oral or inhalation solution is also available on the market. The approved oral dosing of Mucomyst for acetaminophen overdose is as follows after an initial induction of emesis:

Loading dose:	140 mg/kg given orally
Maintenance dose:	70 mg/kg given orally q 4hr for 17 doses

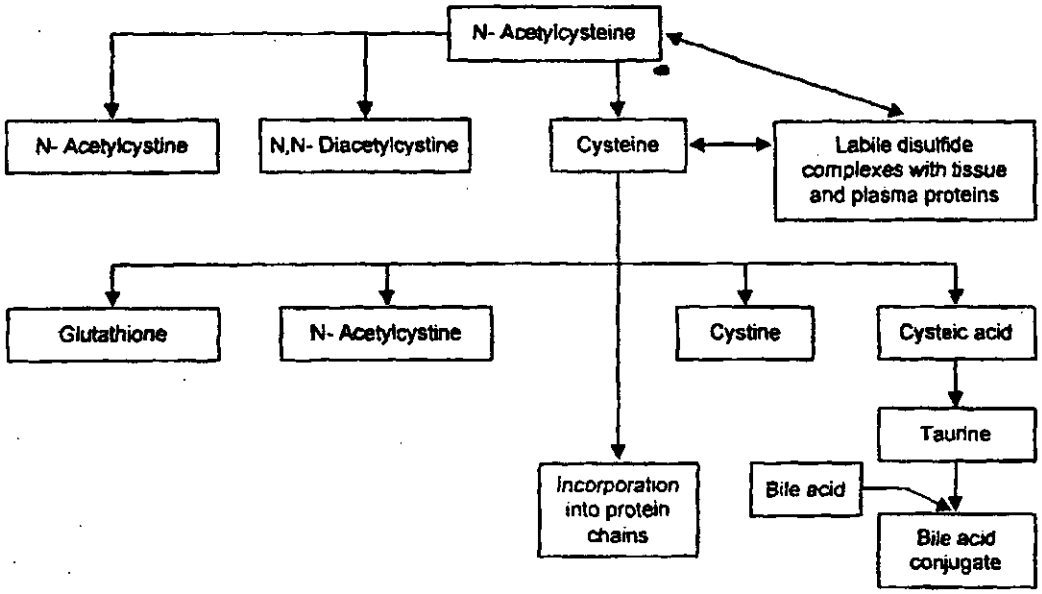
Acetaminophen, which is nontoxic, is extensively metabolized in the liver to form principally the sulfate and glucuronide conjugates which are also nontoxic and are rapidly excreted in the urine. A small fraction of an ingested dose is metabolized in the liver by the cytochrome P-450 mixed function oxidase enzyme system to form a reactive, potentially toxic, intermediate metabolite which preferentially conjugates with hepatic glutathione to form the nontoxic cysteine and mercapturic acid derivatives which are then excreted by the kidney. Therapeutic doses of acetaminophen do not saturate the glucuronide and sulfate conjugation pathways and do not result in the formation of sufficient reactive metabolite to deplete glutathione stores. However, following ingestion of a large overdose (150 mg/kg or greater), the glucuronide and sulfate conjugation pathways are saturated resulting in a larger fraction of the drug being metabolized via the P-450 pathway. The increased formation of reactive metabolite may deplete the hepatic stores of the glutathione with subsequent binding of the metabolite to protein molecules within the hepatocyte resulting in cellular necrosis.

Acetylcysteine has been shown to reduce the extent of liver injury following acetaminophen overdose. Its effectiveness depends on early administration. Acetylcysteine probably protects the liver by maintaining or restoring the glutathione levels, or by acting as an alternate substrate for conjugation with, and thus detoxification of, the reactive metabolite.

Acetylcysteine injection product has been approved outside the US, i.e., Parvolex 20%. Cumberland Pharmaceuticals is seeking approval of Acetadote Injection (Acetylcysteine, 200 mg/ml or 20%) under NDA 21-539. In the Pre-NDA meeting on 12/15/00, OCPB requested that a bridging bioavailability study be performed "if the firm would be relying on a finding of safety and effectiveness for the oral reference product", but added that the oral product would unlikely provide sufficient bioavailability to support the safety and effectiveness of IV formulation. In other words, the extrapolation of oral efficacy/safety to IV use is expected to be very weak.

Acetadote Injection was submitted under 505(b)(2) and granted an orphan drug status on 10/19/01 for IV treatment of moderate to severe acetaminophen overdose. It contains the same formulation (acetylcysteine and EDTA in sterile aqueous solution and NaOH is used to adjust pH) as Parvolex 20% and Mucomyst oral solution without sterilization. The IV administration of acetylcysteine will be useful in patients who are comatose.

The metabolic pathway of acetylcysteine has been proposed in the literature as follows:



As reported in the literature, acetylcysteine can be present in its intact (reduced form) as well as in various oxidized forms, i.e., disulfides (N,N'-diacetylcystine, N-acetylcysteine-cysteine, N-acetylcysteine-glutathione, N-acetylcysteine-protein, etc.). In most of the published articles, total acetylcysteine plasma levels were measured.

From the submitted 14 articles, it is reported that:

1. After an IV dose of Acetylcysteine (200 mg) to 6 healthy volunteers (2M + 4F), it exhibited a three-exponential decay pattern with a mean terminal half-life ($T_{1/2}$) of 5.6 hrs for total acetylcysteine plasma levels. Clearance (CL) was reported to be 0.11 liter/hr/kg and the steady-state volume of distribution (Vd_{ss}) of 0.47 liter/kg. Oral bioavailability for a single dose of 400 mg was also reported to be 9.1% from the same study (Olsson et al, 1988).

2. After an oral dose of ^{35}S-acetylcysteine 100 mg given to 10 patients with respiratory disorders, the total radioactivity reached C_{max} in 2-3 hr and remained high till 24 hrs; about 22% of total radioactivity was excreted in urine after 24 hrs and in the blood, about 17% of total acetylcysteine plasma levels was not protein bound. However, no metabolites were analyzed/ identified (Rodenstein et al, 1978).

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3. In one IV study, in subjects with severe liver damage (cirrhosis) due to alcohol (with Child-Pugh score of 7-13), or 1st and/or 2nd biliary cirrhosis (with Child-Pugh score 5-7) there was significant increase in mean AUC (62%↑, $p<0.05$) and mean $T_{1/2}$ (80% ↑, $p<0.05$) while the mean CL was significantly decreased (30% ↓, $p<0.01$) compared to control group (Jones et al, 1997).

   However, in another study post IV infusion (150 mg/kg infused for 15 min, 50 mg/kg infused for 4 hr, and 100 mg/kg infused for 16 hrs) to patients with acetaminophen ingestion, the mean plasma level of total acetylcysteine at steady state was 32% lower in patients with severe liver damage as compared to patients with mild or no liver damage, yet no appreciable changes were observed in $T_{1/2}$ and CL (Prescott et al, 1989). The author postulated that the unexpected finding may be due to a delay in development of severe liver damage for at least 3 days after overdose of acetaminophen.

4. Renal CL is reported to contribute to 30% of total CL. Regarding renal impairment, no PK information is available in the literature to allow for dose adjustment for this population.

5. No PK study in pediatrics was conducted and no pediatric patients were enrolled in the pivotal clinical trial **CM8801**. Literature information was available on acetylcysteine in pre-term neonates and adolescents. The elimination of acetylcysteine was slowed down and mean $T_{1/2}$ was reported to be doubled (11 hrs; Ahola, 1999).

6. Acetylcysteine was detected in infant's cord blood indicating that the NAC could cross the placenta following IV delivery to pregnant women (Horowitz, 1997).

7. Very little information on acetylcysteine in geriatric population was available.

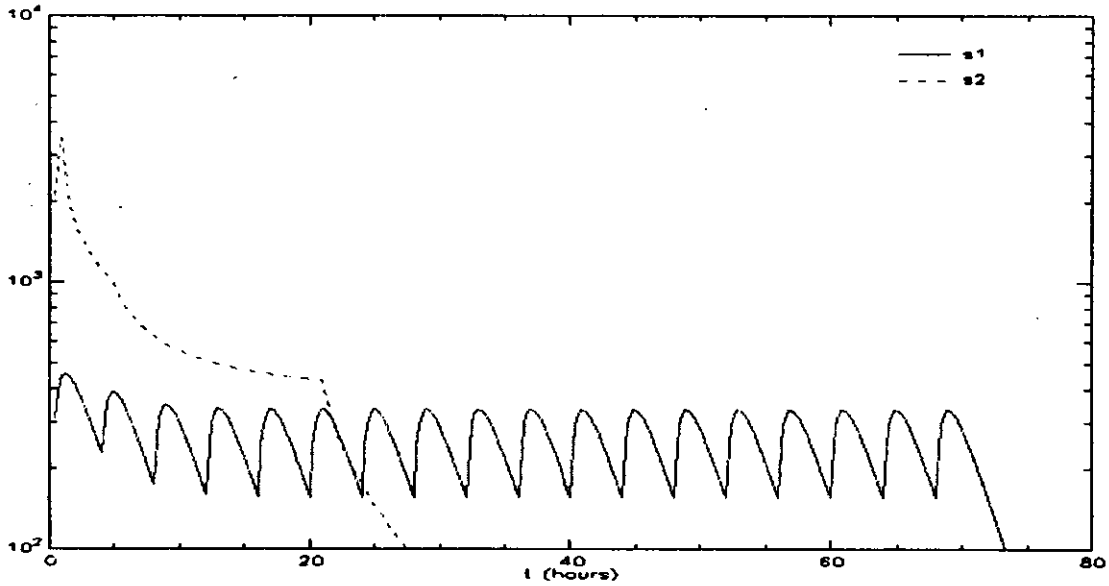
8. For drug-drug interaction, symptomatic hypotension was reported in patients with unstable angina pectoris receiving acetylcysteine and nitroglycerine (Horowits, 1988).

B. General Clinical Pharmacology

1. Is the oral PK data/profile comparable to that for IV dosing regimen in order to extrapolate oral efficacy data for IV use?

Based on literature information, simulations were undertaken in an attempt to extrapolate oral safety/efficacy data for IV route of administration by comparing the acetylcysteine plasma profiles after oral dosing of Mucomyst (with a reported oral bioavailability of around 10%) and those after IV dosing of Acetadote. The simulated results are shown in Figure 1.

Figure 1. Simulation of Mean Total Acetylcysteine Plasma Profiles (μmole/liter vs. hour) Post Oral and IV Dosing



S1 (solid line): Currently approved Oral dosing of Mucomyst
S2 (hatched line): Proposed IV dosing of Acetadote Injection

According to the simulated data, initial total acetylcysteine plasma levels after IV dosing are much higher (at least 10 fold or greater) than those after oral dosing.

Safety data available from the clinical database would need to support the fact that the predicted total acetylcysteine plasma levels from the proposed IV dosing of Acetadote are safe. In terms of efficacy, systemic plasma levels are thought NOT to be important. After oral dosing (as currently approved), total acetylcysteine levels in the liver would be expected to be higher than that circulating/systemic plasma levels; this is not necessarily the case post IV dosing. This renders **impossible any** attempts to extrapolate oral efficacy data for IV efficacy using PK simulations with currently available information.

2. Is adjustment for Acetylcysteine IV dose needed for special populations or due to drug-drug interactions?

Adequate information is not available to assess the need for dosage adjustment in special populations.

I. Intrinsic factors:

1. Gender:
   Adequate information is not available to assess if there are differences in PK between males and females.

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2. Hepatic Impairment:

In subjects with severe liver damage, i.e., cirrhosis due to alcohol (with Child-Pugh score of 7-13), or 1st and/or 2nd biliary cirrhosis (with Child-Pugh score of 5-7), mean $T_{1/2}$ increased by 80% while mean CL decreased by 30% compared to control group.

3. Renal Impairment:
PK information is not available on the PK in patients with renal impairment.

4. Pediatrics:
The elimination of acetylcysteine is much slower in new-borns (mean $T_{1/2}$ of 11 hours) than in adults (5.6 hours). Pharmacokinetic information is not available in other age groups.

5. Geriatrics:
Inadequate information on acetylcysteine PK (or clinical use) in geriatric patients was available.

6. Pregnancy:
In pregnant women receiving acetylsycteine treatment for acetaminophen toxicity, acetylcysteine was detected in the cord blood of the 3 viable infants and in cardiac blood of the fourth infant, sampled at a time of autopsy indicating that acetylcysteine can across placenta.

II. Extrinsic Factor:

1. Drug-Drug Interaction (DDI):

No DDI studies have been conducted.

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V. Detailed Labeling Recommendations

Please see the attached PI for details in Appendix 1.

VI. Appendices

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Appendix 1

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Proposed Package Insert (06/22/02 Version) and OCPB Recommendations

12 page(s) of draft labeling has been removed from this portion of the review.

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Appendix 2

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References cited in Item 6 (Human PK/Bio Section)

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

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

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

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

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

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

7. Holdiness MR. Clinical pharmacokinetics of N-acetylcysteine. Clin Pharmacokinet 1991:20(2):123-34.

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

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

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

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

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

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

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

Appendix 3

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-539	Brand Name	Acetadote
OCPB Division (I, II, III)	II	Generic Name	Acetylcysteine
Medical Division	GI & Coagulation	Drug Class	Naturally occurring amino acid
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	[redacted]
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Sterile Solution
		Dosing Regimen	For IV: 150 mg/kg infused over [redacted] 50 mg/kg infused over 4 hrs, and then 100 mg/kg infused over 16 hrs.
Date of Submission	06/27/02	Route of Administration	IV
Estimated Due Date of OCPB Review	11/01/02	Sponsor	Cumberland
Medical Division Due Date	12/01/02	Priority Classification	P
PDUFA Due Date	01/01/03		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	[redacted]			
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
1. Clinical Pharmacology	[redacted]	[redacted]		
Mass balance:		1		Literature data
Isozyme characterization:		0		
Blood/plasma ratio:		0		
Plasma protein binding:		0		
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]		
Healthy Volunteers-	[redacted]	[redacted]		
single dose:		1		Literature Data
multiple dose:		0		
Patients-	[redacted]	[redacted]		
single dose:		1		Literature Data
multiple dose:		0		
Dose proportionality -	[redacted]	[redacted]		
fasting / non-fasting single dose:		0		
fasting / non-fasting multiple dose:		1		Literature Data (oral data)
Drug-drug interaction studies -	[redacted]	[redacted]		
In-vivo effects on primary drug:		0		
In-vivo effects of primary drug:		1		Literature Data
In-vitro:		0		
Subpopulation studies -	[redacted]	[redacted]		
ethnicity:		0		
gender:		0		
pediatrics:		1		Literature Data
geriatrics:		0		
renal impairment:		0		
hepatic impairment:		1		Literature Data
PD:	[redacted]	[redacted]		
Phase 2:		0		
Phase 3:		0		
PK/PD:	[redacted]	[redacted]		
Phase 1 and/or 2, proof of concept:		0		
Phase 3 clinical trial:		0		
Population Analyses -	[redacted]	[redacted]		

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Data rich:		—	—	
Data sparse:		—	—	
II. Biopharmaceutics	[redacted]	[redacted]		
Absolute bioavailability:	X	2		**Literature Data**
Relative bioavailability -	[redacted]	[redacted]		
solution as reference:		0		
Alternate formulation as reference:		0		
Bioequivalence studies -	[redacted]	[redacted]		
Traditional design; single / multi dose:		0		
Replicate design; single / multi dose:		0		
Food-drug interaction studies:	N/A	0		
Dissolution:	N/A	0		
(IVIVC):		0		
Bio-wavier request based on BCS		0		
BCS class				
III. Other CPB Studies	[redacted]			
Genotype/phenotype studies:		0		
Chronopharmacokinetics		0		
Pediatric development plan		0		
Literature References		5		
Total Number of Studies		14		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ? No!	**Needs to be sent**	An article(s) published in Arzneimittel forschung 1989; 39:382-6 had different authors, by DeCaro L. et al (under PK section reference on page 35, Vol. 1.6) and by Holdiness MR. (under annotated Labeling reference on page 22, Vol. 1.3). Please provide clarification if this is the same or different article(s) . If they are different, please provide the location of the article by Holdiness MR. (page # and vol. #) or submit the article for review.
QBR questions (key issues to be considered)	**Do the published articles support the labeling of this NDA?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Tien-Mien Chen, Ph.D. 08/07/02**	
Secondary reviewer Signature and Date	**Suresh Doddapaneni, Ph.D. 08/07/02**	

CC: NDA 21-539, HFD-850 (Electronic Entry or Lee), HFD-180 (R. Prizont, B. Strongin), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski), CDR (Z. Zadeng)

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/s/

Tien-Mien Chen
12/4/02 04:02:30 PM
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Suresh Doddapaneni
12/6/02 08:21:18 AM
BIOPHARMACEUTICS

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