CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-539

CHEMISTRY REVIEW(S)

CDER **CHEMISTRY REVIEW** CDER

Chemistry Review Data Sheet

NDA 21-539

Acetadote (Acetylcysteine) Injection

Cumberland Pharmaceuticals

Ali Al-Hakim, Ph.D.
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

CHEMISTRY REVIEW

Chemistry Review Data Sheet

1. NDA No. 21-539

2. REVIEW #: 2

3. REVIEW DATE: January 09, 2003

4. REVIEWER: Ali Al-Hakim

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	June 27, 2002
Amendment (AC)	October 15, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Responses to IR Chemistry letter dated 12/10/02	December 20, 2003
Additional Responses	March 07, 2003
Amendment (responses)	November 19, 2003
Amendment (Micro responses)	October24, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Cumberland Pharmaceuticals

Address: 209 10TH Avenue South
Suite 332
Nashville, Tennessee 37203

Representative: A.J. Kazimi

Telephone: 615 255 0068

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Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Acetadote
b) Non-Proprietary Name (USAN):	Acetylcysteine
c) Code Name/# (ONDC only):	Not provided
d) Chem. Type/Submission Priority	(ONDC only):
• Chem. Type:	3
• Submission Priority:	P & V

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antidote for hepatotoxic quantity of Acetaminophen

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 10 mL and 30mL

13. ROUTE OF ADMINISTRATION: Intravenous injection

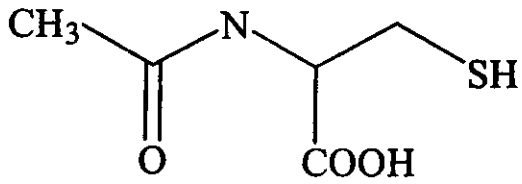
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical Names:	N-Acetylcysteine and	N-acetyl-L-cysteine
Molecular Weight	163.2 g/mol	
Chemical Formula	$C_5H_9NO_3S$	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]					Adequate	01/02/04	Adequate responses were received to our deficiency letter dated November 06, 2002.
					Adequate	12/27/02	M.Shih HFD-643 No revision for this item since last review
[redacted]					Adequate	10/26/00	A.Raw HFD-623 No revision for this item since last review

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

Chemistry Review Data Sheet

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		Tom Permutt
EES	Acceptable	08-05-2002	
Pharm/Tox	Acceptable		Ke Zhang
Biopharm	Pending		Tien-Mien Chen
LNC	N/A		
Methods Validation	Pending		
OPDRA	Acceptable	09/16/02	
EA	N/A*		
Microbiology	Acceptable		David Hussong

* The EA information was provided in the NDA and included in this review (see Environmental Assessment section).

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.
____ Yes ____ No If no, explain reason(s) below:

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The Chemistry Review for NDA 21-539

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The first CMC review for the NDA, dated December 10, 2002, recommended that the application should be approvable pending additional and satisfactory information. In July 21, 2002, , the NDA applicant submitted amendment which contains satisfactory responses to the FDA the requests (Evaluation of the responses included in this submission). In addition, the drug substance manufacturer provided satisfactory responses to the DMF Deficiency letter (see supporting documents table).

Therefore, the application is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

Phase 4 (Post-Marketing) Commitment

1- Conduct a study regarding the impact of decreasing or removing Edetate from the drug product formulation on:
   a) stability program
   b) compatibility protocol using infusing bags

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product Acetadote® (N-acetylcysteine) Injection is used for the treatment of acetaminophen overdose. Acetadote is supplied in a sterile solution in **vials** (two strengths of **10 mL** and **30mL**) containing 20% w/v (200mg/mL acetylcysteine). The pH of the solution ranges from 6.0 to 7.5. Acetadote® contains the following inactive ingredients: disodium edetate, sodium hydroxide, and water for injection. The drug product is packaged in glass I type USP vials using [redacted] stoppers. Acetylcysteine solution, USP solution is analyzed according to the current USP and BP monographs.

The iv use of the drug product is approved for the treatment of acetaminophen overdose in UK, Australia, New Zealand and Canada.. The iv formulation of the drug product used in the above countries is identical to the proposed formulation described in this NDA.

The drug product is sold in Canada in 10 ml ampules and 10 and 30 mL vials. Bioniche has been manufacturing and selling Parvolex on the Canadian market since 1993. Bioniche purchased the rights to the name and manufacturing the product from Glaxo in 1993. Glaxo had been marketing the product since July 1981.

B. Description of How the Drug Product is Intended to be Used

Acetadote® is indicated for iv treatment [redacted] Acetadote should be administered immediately if 24 hours or less have elapsed from the injection time of overdoes. **The following steps are recommended for injection use:**

Loading Dose: 150mg/kg in 200 mL of 5% dextrose, infuse intravenously over [redacted]

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

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C. Basis for Approvability or Not-Approval Recommendation

The first CMC review for the NDA, dated December 10, 2002, recommended that the application should be approvable pending additional and satisfactory information to the FDA questions. These question are related to manufacturing process, proposed test methods and specifications, container/closure system, stability, labeling (———————) and compatibility with 5% dextrose infusion solution.

In July 21, 2002, , the NDA applicant submitted amendment which contains satisfactory responses to the FDA the requests (review and subsequent evaluation of these responses are included in this submission).

III. Administrative

A. Reviewer's Signature
Ali Al-Hakim, Ph.D.

B. Endorsement Block
Ali Al-Hakim, 01/09/03
Liang Zhou, 01/09/03
Paul Levine, 01/09/03

C. CC Block
HFD-180/ NDA 21-539
HFD-180/B.Justice
HFD/180/P. Levine
HFD/180/L.Zhou
HFD/180/A.Al-Hakim
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/s/

Ali Al-Hakim
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CHEMIST

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NDA 21-539

Acetadote (Acetylcysteine) Injection

Cumberland Pharmaceuticals

Ali Al-Hakim, Ph.D.
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

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Chemistry Review Data Sheet

1. NDA 21-539

2. REVIEW #: 1

3. REVIEW DATE: 04-Dec-2002

4. REVIEWER: Ali Al-Hakim

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	June 27, 2002
Amendment (AC)	October 15, 2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Cumberland Pharmaceuticals
Address:	209 10TH Avenue South Suite 332 Nashville, Tennessee 37203
Representative:	A.J. Kazimi
Telephone:	615 255 0068

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Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Acetadote
b) Non-Proprietary Name (USAN): Acetylcysteine
c) Code Name/# (ONDC only): Not provided
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: P & V

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antidote for hepatotoxic quantity of Acetaminophen

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 10 mL and 30mL

13. ROUTE OF ADMINISTRATION: Intravenous injection

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15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

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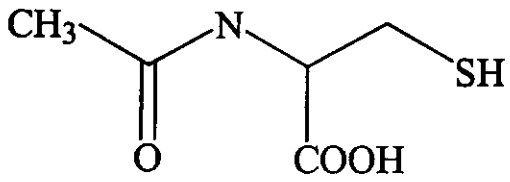

Chemical Names: N-Acetylcysteine and N-acetyl-L-cysteine
Molecular Weight 163.2 g/mol
Chemical Formula $C_5H_9NO_3S$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	[redacted]		[redacted]		inadequate	10/25/02	This is the first review for this DMF

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

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CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		Tom Permutt
EES	Acceptable	08-05-2002	
Pharm/Tox	Acceptable		Ke Zhang
Biopharm	Pending		Tien-Mien Chen
LNC	N/A		
Methods Validation	Pending		
OPDRA	Acceptable	09/16/02	
EA	N/A*		
Microbiology	Pending		David Hussong

* The EA information was provided in the NDA and included in this review (see Environmental Assessment section).

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.
____ Yes ____ No If no, explain reason(s) below:

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ON ORIGINAL

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The Chemistry Review for NDA 21-539

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The application is approvable from the Chemistry Manufacturing and Control point of view. There are various deficiencies delineated in the Chemistry Discipline Letter at the end of this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product Acetadote® (N-acetylcysteine) Injection is used for the treatment of acetaminophen overdose. Acetadote is supplied in a sterile solution in vials (two strengths of 10 mL and 30mL) containing 20% w/v (200mg/mL acetylcysteine). The pH of the solution ranges from 6.0 to 7.5. Acetadote® contains the following inactive ingredients: disodium edetate, sodium hydroxide, and water for injection. The drug product is packaged in glass I type USP vials using ——— stoppers. Acetylcysteine solution, USP solution is analyzed according to the current USP and BP monographs. The iv use of the drug product is approved for the treatment of acetaminophen overdose in UK, Australia, New Zealand and Canada.. The iv formulation of the drug product used in the above countries is identical to the proposed formulation described in this NDA.

The drug product is sold in Canada in 10 ml ampules and 10 and 30 mL vials. Bioniche has been manufacturing and selling Parvolex on the Canadian market since 1993. Bioniche purchased the rights to the name and manufacturing the product from Glaxo in 1993. Glaxo had been marketing the product since July 1981.

The drug substance is N-acetylcysteine, USP ———

B. Description of How the Drug Product is Intended to be Used

Acetadote® is indicated for iv treatment ———

Acetadote should be administered immediately if 24 hours or less have elapsed from the injection time of overdoes. **The following steps are recommended for injection use:**

Loading Dose: 150mg/kg in 200 mL of 5% dextrose, infuse intravenously over —

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

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C. Basis for Approvability or Not-Approval Recommendation

The application is approvable pending that the NDA applicant and the drug substance DMF holder provided adequate responses to the deficiencies delineated in the chemistry discipline letter at the end of this review. The main deficiencies are related to manufacturing process, proposed test methods and specifications, container/closure system, stability, labeling ( ) and compatibility with 5% dextrose infusion solution

The applicant claimed that the drug substance meets USP specifications, however, there is not enough sufficient test data to support this claim because the drug substance used as an injectable drug product.

APPEARS THIS WAY
ON ORIGINAL

III. Administrative

A. Reviewer's Signature
Ali Al-Hakim, Ph.D.

B. Endorsement Block
Ali Al-Hakim, 12/04/02
Liang Zhou, 12/04/02
Brian Strongin, 12/04/02

C. CC Block
HFD-180/ NDA 21-539
HFD-180/B.Justice
HFD/180/B.Strongin
HFD/180/L.Zhou
HFD/180/A.Al-Hakim
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