CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-777

CHEMISTRY REVIEW(S)

NDA 21-777

Amrix®
(cyclobenzaprine hydrochloride extended-release capsules)

ECR Pharmaceuticals, Inc.

Sue-Ching Lin

Review Chemist

Office of New Drug Quality Assessment
Pre-Marketing Division III, Branch V
for
Division of Anesthesia, Analgesia, and
Rheumatology Products (DAARP)

Table of Contents

CMC Review Data Sheet

1. NDA 21-777

2. REVIEW #: 2

3. REVIEW DATE: 26-Jan-2007

4. REVIEWER: Sue-Ching Lin

5. PREVIOUS DOCUMENTS:

Submissions Reviewed in CMC Review #1	Document Date
Original Submission	29-Apr-2004
Amendment (BC)	29-Jun-2004
Amendment (BC)	30-Jul-2004
Amendment (BC)	04-Oct-2004
Amendment (BZ)	10-Dec-2004
Amendment (BC)	17-Dec-2004
Amendment (BC)	16-Feb-2005

6. SUBMISSION(S) BEING REVIEWED:

Subject of this Review	Document Date
Resubmission (AZ)	05-Augr-2006
Amendment (BC) (response to 9/11/06 CMC IR)	19-Sep-2006
Amendment (BC) (response to 10/2/06 & 10/4/06 IR)	22-Nov-2006
Amendment (BL) (response to 1/4/07 CMC & DMETS IR)	12-Jan-2007
Amendment (BL) (response to 1/17/07 CMC IR)	23-Jan-2007
Amendment (BL) (response to1/24/07 CMC IR)	25-Jan-2007

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	ECR Pharmaceuticals, Inc.
Address:	P.O. Box 71600 Richmond, Virginia 23255
Representative:	[redacted]
Telephone:	[redacted]

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Amrix®
b) Non-Proprietary Name: cyclobenzaprine hydrochloride extended-release capsules
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

List Drug: Flexeril® tablet, 10 mg, McNeil Consumer & Specialty Pharmaceuticals, NDA 17-821

10. PHARMACOL. CATEGORY: muscle relaxants

11. DOSAGE FORM: capsule, extended-release

12. STRENGTH/POTENCY: 15 mg and 30 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: √ Rx ___ OTC

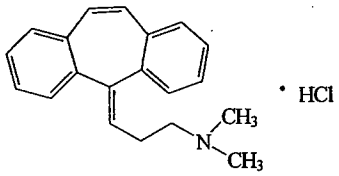
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

√ Not a SPOTS product

CMC Review Data Sheet

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

3-(5*H*-dibenzo[a,d]-cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine, hydrochloride



• HCl

$C_{20}H_{21}N \bullet HCl$, MW 311.85

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Adequate	1/31/06	Reviewed by Guoping Sun
					Adequate	8/16/01	Rajendra Uppoor
					Adequate	7/26/04	Li Shan Hsieh
					N/A		*
					Adequate	9/23/97	*
					N/A		*
					N/A		*
					N/A		*
					N/A		*
					N/A		*
					Adequate	6/19/03	*
					Adequate	2/20/04	*

* See page 38 of CMC review #1 under container closure system for details

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

CMC Review Data Sheet

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
IND	62,261	cyclobenzaprine hydrochloride capsules
NDA	17-821	Flexeril® Tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	10/18/06	J.D. Ambrogio
Pharm/Tox	N/A		
Clinical Pharmacology	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS*	The proposed proprietary name Amrix® is acceptable	12/28/06	Richard Abate
EA	Categorical exclusion (see review #1)	2/17/05	Sue-Ching Lin
Microbiology	N/A		

* Division of Medication Errors and Technical Support

Executive Summary Section

The CMC Review for NDA 21-777

The Executive Summary

I. RECOMMENDATIONS

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls perspective, this NDA is recommended for approval.

The following statement should be included in the approval letter:

"A shelf life of 24 months is granted for this drug product."

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

None

II. SUMMARY OF CMC ASSESSMENTS

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

(1) Drug Substance

The active ingredient is cyclobenzaprine hydrochloride, USP. It is manufactured by [redacted] Detailed information on the drug substance is referenced to DMF [redacted], which was reviewed on 1/28/05 by this reviewer in the first review cycle and found to be adequate to support this NDA. The subsequent amendments were reviewed and found acceptable by OGD on 1/31/06. The drug substance meets the current USP monograph for cyclobenzaprine hydrochloride and additional testing for impurities in accordance with ICH Q3A recommendations.

(2) Drug Product

The drug product is formulated in two strengths, 15 mg/capsule and 30 mg/capsule. [redacted]

[redacted] Both strengths of the drug product are packaged in bottles of 60 capsules.

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

The drug product is intended to be administered once daily and will be dispensed by prescription only. It is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Use of Amrix for periods longer than two or three weeks is not recommended.

The submitted drug product stability data include long-term stability data for 36 months and accelerated stability data for 6 months on three registration batches of drug product (manufactured using the drug substance from ——— and up to 24 months of stability data on a batch manufactured using the drug substance from ——— the intended supplier of the drug substance for commercial manufacture. Therefore, based on the submitted stability data, an expiration period of 24 months can be granted. (The original submission proposed a 24-month expiration period. This resubmission did not request an extension of shelf life.)

C. Basis for Approvability or Not-Approval Recommendation

The CMC information of the drug substance was referenced to DMF——which was found to be adequate to support this NDA.

The applicant has adequately responded to the deficiency regarding drug release acceptance criteria, which was included in the FDA's "approvable" letter dated February 28, 2005.

The manufacture process, the control of excipients, and the specification are adequate to ensure consistency in the quality of the drug product. The packaging materials were found to be adequate.

A re-evaluation of all the facilities for the manufacture and control of the drug substance and drug product was submitted by this reviewer to the Office of Compliance. An overall acceptable recommendation was issued by the Office of Compliance on 10/18/06.

The Division of Medication Errors and Technical Support (DMETS) has no objections to the use of the proposed proprietary name, Amrix.

Updated labeling was submitted in this review cycle. Labeling deficiencies that were identified by this reviewer have been adequately addressed by the applicant in the amendments.

Executive Summary Section

III. ADMINISTRATIVE

A. Reviewer's Signature: electronically signed in DFS

Sue-Ching Lin, M.S., R.Ph.

B. Endorsement Block: electronically signed in DFS

Ravi Harapanhalli, Ph.D.

C. CC Block: entered electronically in DFS

21 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-1

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/s/

Sue Ching Lin
1/29/2007 06:58:38 PM
CHEMIST

Ravi Harapanhalli
1/29/2007 08:31:06 PM
CHEMIST

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NDA 21-777

Amrix
(cyclobenzaprine hydrochloride extended-release capsules)

ECR Pharmaceuticals, Inc.

Sue-Ching Lin

Review Chemist

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drugs, HFD-550

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Chemistry Review Data Sheet

1. NDA 21-777

2. REVIEW #: 1

3. REVIEW DATE: 16-Feb-2005

4. REVIEWER: Sue-Ching Lin

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	29-Apr-2004
Amendment (BC)	29-Jun-2004
Amendment (BC)	30-Jul-2004
Amendment (BC)	04-Oct-2004
Amendment (BZ)	10-Dec-2004
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Amendment (BC)	16-Feb-2005

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Name: ECR Pharmaceuticals, Inc.
Address: P.O. Box 71600
Richmond, Virginia 23255
Representative:

Telephone:

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Amrix

b) Non-Proprietary Name (USAN): cyclobenzaprine hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

List Drug: Flexeril® tablet, 10 mg, McNeil Consumer & Specialty Pharmaceuticals, NDA 17-821

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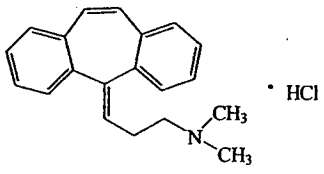

$C_{20}H_{21}N \cdot HCl$, MW 311.85

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					Adequate	8/16/01	
					Adequate	7/26/04	
					N/A		*See page 38
					Adequate	9/23/97	*See page 38
					N/A		*See page 38
					N/A		*See page 38
					N/A		*See page 38
					N/A		*See page 38
					N/A		*See page 38
					Adequate	6/19/03	*See page 38
					Adequate	2/20/04	*See page 38

* See page 38 of this review under container closure system for details

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[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:

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18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	1/24/05	J.D. Ambrogio
Pharm/Tox	N/A		
Clinical Pharmacology	Dissolution acceptance criteria & method. See clinical pharmacology review.	2/15/05	Abi Adebowale
LNC	N/A		
Methods Validation	N/A, according to the current ONDC policy		
Office of Drug Safety	The proposed proprietary name Amrix is acceptable	12/10/04	Kimberly Culley
EA	Categorical exclusion (see review)		
Microbiology	N/A		

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The Chemistry Review for NDA 21-777

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective, this NDA is recommended for approval.

Please refer to the clinical pharmacology reviewer's recommendation on the acceptance criteria for the drug release test. Some of the labeling comments will need to be conveyed to the applicant, if there is a resubmission to this NDA (see the next page under Basis of Approvability).

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

None

II. Summary of Chemistry Assessments

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

(1) Drug Substance

The active ingredient is cyclobenzaprine hydrochloride, USP. It is manufactured by [redacted]. Detailed information on the drug substance is referenced to [redacted], which was reviewed on 1/28/05 by this reviewer and found to be adequate to support this NDA. The drug substance meets the current USP monograph for cyclobenzaprine hydrochloride and additional testing for impurities in accordance with ICH Q3A recommendations.

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The submitted drug product stability data include long-term stability data for 12 months and accelerated stability data for 6 months on three registration batches of drug product and up to 24 months of supportive data on pivotal clinical batches (same formulation). The data support the proposed 24-month expiration period for the drug product stored at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

The CMC information of the drug substance was referenced to DMF ←——, which was reviewed by this reviewer on 1/28/05 and found to be adequate to support this NDA.

The manufacture process, the control of excipients, and the specification are adequate to ensure consistency in the quality of the drug product. The packaging materials were found to be adequate.

The Office of Compliance has issued "acceptable" recommendation for each facility used for manufacturing and control of the drug substance and drug product.

The Office of Drug Safety has no objections to the use of the proposed proprietary name, Amrix.

The clinical pharmacology reviewer recommended tightening the acceptance criteria for the drug release test. Refer to clinical pharmacology review and page 27 of this review.

Some of the comments regarding labeling (pages 47 to 49 of this review) have not been conveyed to the applicant per the suggestion from Carmen DeBellas, Chief Project Manger. The Division has decided that this NDA will not be approved due to major clinical deficiencies and thus there will be no labeling negotiation with the applicant. However, these labeling comments will need to be communicated to the applicant, along with the recommended acceptance criteria for the drug release test, if there is a resubmission to this NDA.

III. Administrative

A. Reviewer's Signature	In DFS
B. Endorsement Block	In DFS
C. CC Block	In DFS

42 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2

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

/s/

Sue Ching Lin
2/17/05 11:35:57 AM
CHEMIST

John Smith
2/17/05 12:04:01 PM
CHEMIST

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6 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 3