# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-777**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

# PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

***For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use***

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
*See OMB Statement on Page 3.*

NDA NUMBER
21-777

NAME OF APPLICANT / NDA HOLDER
E. Claiborne Robins Company, Inc.
DBA ECR Pharmaceuticals

***The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.***

TRADE NAME (OR PROPOSED TRADE NAME)
Amrix

| ACTIVE INGREDIENT(S) | STRENGTH(S) |
|---|---|
| Cyclobenzaprine Hydrochloride | 15 mg Extended Release Capsules<br>30 mg Extended Release Capsules |

DOSAGE FORM
Extended Release Capsules

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

***FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.***

***For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.***

## 1 GENERAL

| | | |
|---|---|---|
| a. United States Patent Number | b. Issue Date of Patent | c. Expiration Date of Patent |
| d. Name of Patent Owner | Address *(of Patent Owner)* | |
| | City/State | |
| | ZIP Code | FAX Number *(if available)* |
| | Telephone Number | E-Mail Address *(if available)* |
| e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞ | Address *(of agent or representative named in 1.e.)* | |
| | City/State | |
| | ZIP Code | FAX Number *(if available)* |
| | Telephone Number | E-Mail Address *(if available)* |

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No



PSC Media Arts (301) 443-1090 EF

***For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.***

## 2. Drug Substance (Active Ingredient)

| | | | |
|---|---|---|---|
| **2.1** | Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? | ☐ Yes | ☐ No |
| **2.2** | Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? | ☐ Yes | ☐ No |
| **2.3** | If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). | ☐ Yes | ☐ No |
| **2.4** | Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**. | | |
| **2.5** | Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) | ☐ Yes | ☐ No |
| **2.6** | Does the patent claim only an intermediate? | ☐ Yes | ☐ No |
| **2.7** | If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | ☐ Yes | ☐ No |

## 3. Drug Product (Composition/Formulation)

| | | | |
|---|---|---|---|
| **3.1** | Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? | ☐ Yes | ☐ No |
| **3.2** | Does the patent claim only an intermediate? | ☐ Yes | ☐ No |
| **3.3** | If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | ☐ Yes | ☐ No |

## 4. Method of Use

***Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:***

| | | | |
|---|---|---|---|
| **4.1** | Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? | ☐ Yes | ☐ No |
| **4.2** | Patent Claim Number *(as listed in the patent)* | Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No | |
| **4.2a** | If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. | Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* | |

## 5. No Relevant Patents

| | | |
|---|---|---|
| For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. | ☒ Yes | |

## 6. Declaration/Certification

**6.1** ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

***Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.***

| 6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)* | Date Signed |
|---|---|
| Davis S. Caskey | 1/14/2005 |

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

| | |
|---|---|
| ☒ NDA Applicant/Holder | ☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official |
| ☐ Patent Owner | ☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official |

| | |
|---|---|
| Name<br>Davis S. Caskey Officer, ECR Pharmaceuticals | |
| Address<br>3969 Deep Rock Road | City/State<br>Richmond, Virginia |
| ZIP Code<br>23233 | Telephone Number<br>804-527-1950 |
| FAX Number *(if available)*<br>804-527-1959 | E-Mail Address *(if available)*<br>davis.caskey@ecrpharma.com |



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# EXCLUSIVITY SUMMARY

NDA # 21-777 SUPPL # HFD # 170

Trade Name Amrix Extended-Release Capsules

Generic Name cyclobenzaprine hydrochloride

Applicant Name ECR Pharmaceuticals

Approval Date, If Known February XX, 2007

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3-years, plus an additional 18 months

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

## PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 1105, Study 1106

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

| | | |
|---|---|---|
| Investigation #1 | | ! |
| | | ! |
| IND # 62,261 | YES ☒ | ! NO ☐ |
| | | ! Explain: |
| Investigation #2 | | ! |
| | | ! |
| IND # 62,261 | YES ☒ | ! NO ☐ |
| | | ! Explain: |

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

| | |
|---|---|
| Investigation #2 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

---

Name of person completing form: Lisa Malandro
Title: Regulatory Health Project Manager
Date: January 26, 2007

Name of Office/Division Director signing form: Bob A. Rappaport, M.D.
Title: Director, Division of Anesthesia, Analgesia and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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ECR PHARMACEUTICALS

ECR PHARMACEUTICALS
P.O. BOX 71600
RICHMOND, VIRGINIA 23255
Tel: (804) 527-1950 Fax: (804) 527-1959

April 2, 2004

Jonca C. Bull, MD
Division Director
Department. of Human Services
Food and Drug Administration
Rockville, MD 20850

Ref: IND 62,261

Dear Dr. Bull:

Since the initial pre-INDA meeting and discussions regarding the necessary requirements for submission of an NDA for the drug product which is the subject of this application (Cyclobenzaprine HCl, Modified Release), additional testing and clinical work above that initially outlined has been completed which we believe has added substantially to the body of knowledge concerning this drug entity and its use. Accordingly, the sponsor of this submission, ECR Pharmaceuticals, requests that the Food and Drug Administration consider and grant an additional period of exclusivity for this product as a result of this additional work and substantial expense.

This request is based on the following work which was completed in addition to the required basic clinical studies and two well controlled clinical trials.

1. ECR completed a genotoxicity battery for this long established chemical entity. This additional work required approximately 8 months to complete, delaying submission and adding notable costs to the project. This additional work provided information which had not been previously completed for this drug entity, even though the product has been marketed for approximately 25 years.

2. ECR developed and tested a lower than previously approved dosage (15 mg total daily dosage) and included this arm in its clinical studies to provide better dosing range information in regard to both efficacy and safety. The inclusion of this additional dosage form increased the scope and costs of the affected clinical trials by about 25% in addition to the added time requirement. This work has provided guidance regarding the most effective use of this drug entity.

3. To further enhance the body of knowledge for this drug in regard to its use in older patients whose metabolism may have slowed or become impaired, ECR expanded a pharmacokinetic trial to include a sufficient number of patients above the age of 65 years to demonstrate possible pharmacokinetic differences. This expansion added both cost and time toward completion of the project. We believe the information gained from this additional work will further enhance the appropriate use of this drug entity, notably in older patients.

*Quality Products at a Price the Patient Can Afford*

Jonca C. Bull, MD
Page Two
April 6, 2004

The above additional work has added approximately 20 months to the anticipated time required for submission, combined with substantial additional project costs. We request that the FDA consider granting an additional period of 18 months of exclusivity above the usual three year period provided for this type of NDA. Such will allow our firm to recoup its developmental costs over a slightly longer period and enable us to come to market with a lower cost product. Please convey this request to the appropriate personnel for evaluation and response.

Sincerely,

Davis S. Caskey
Vice President
Pharmaceutical Operations

DSC/jh

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# PEDIATRIC PAGE

**NDA/BLA # :** 21-777 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

**Stamp Date:** April 29, 2004 **PDUFA Goal Date:** 2/7/07

**HFD** 170 **Trade and generic names/dosage form:** AMRIX (cyclobenzaprine hydrochloride) Extended-Release Capsules, 15 and 30 mg

**Applicant:** ECR Pharmaceuticals **Therapeutic Class:** muscle relaxant

**Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? ***

- X Yes. Please proceed to the next question.
- ☐ No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

**Indication(s)** ***previously approved*** **(please complete this section for supplements only):** _____

**Each indication covered by current application under review must have pediatric studies:** ***Completed, Deferred, and/or Waived.***

**Number of indications for this application:** 1

**Indication #1:** _____

**Is this an orphan indication?**

- ☐ Yes. PREA does not apply. Skip to signature block.
- X No. Please proceed to the next question.

**Is there a full waiver for this indication (check one)?**

- X Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed

**NOTE: More than one may apply**

**Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason for full waiver:**

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- X Other: This formulation offers no advantage for pediatric patients over existing immediate-release formulations and offers less dosing flexibility.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived (fill in applicable criteria below):**

**Min_____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Reason(s) for partial waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred (fill in applicable criteria below):**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

**Other:**_____

**Date studies are due (mm/dd/yy):** _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies (fill in applicable criteria below):**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Comments:**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

*{See appended electronic signature page}*

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

## Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** _____

**Is this an orphan indication?**

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

**Is there a full waiver for this indication (check one)?**

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  **NOTE: More than one may apply**
  **Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason(s) for full waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived (fill in applicable criteria below)::**

**Min** _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
**Max**_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

**Reason(s) for partial waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

*complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred (fill in applicable criteria below)::**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

**Date studies are due (mm/dd/yy):** _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies (fill in applicable criteria below):**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Comments:**

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.***

**This page was completed by:**

*{See appended electronic signature page}*

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

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On Original

ECR PHARMACEUTICALS
P.O. BOX 71600
RICHMOND, VIRGINIA 23255
Tel: (804) 527-1950 Fax: (804) 527-1959

Reference: NDA #21-777

To Whom It May Concern:

E. Claiborne Robins Company, Inc. (dba ECR Pharmaceuticals) hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Attested to by:

Davis S. Caskey
Vice President, Officer

14 January 2005
Date

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

*TO BE COMPLETED BY APPLICANT*

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

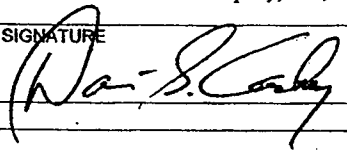
*Please mark the applicable checkbox.*

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| Clinical Investigators | | |
|---|---|---|
| | See Attached | |
| | | |
| | | |

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| NAME | TITLE |
|---|---|
| Davis Caskey | Vice President, Pharmaceutical Operations |
| **FIRM / ORGANIZATION** | |
| E. Claiborne Robins Company, Inc., DBA ECR Pharmaceuticals | |
| **SIGNATURE** | **DATE** |
|  | 4/29/04 |

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

## List of Investigators Sorted by Study Number

| Study No. | Site No. | Principal Investigator | Sub-Investigators |
|---|---|---|---|
| 1101 | 1 | Lawrence A. Galitz, MD<br>SFBC International, Inc.<br>11190 Biscayne Blvd.<br>Miami, FL 33181 | |
| 1102 | 1 | Maria Josefa Gutierrez, MD<br>CNS Clinical Trials<br>108 NE 1st St.<br>Fort Lauderdale, FL 33301 | |
| 1103 | 1 | Maria Josefa Gutierrez, MD<br>CNS Clinical Trials<br>108 NE 1st St.<br>Fort Lauderdale, FL 33301 | |
| 1104 | 1 | Maria Josefa Gutierrez, MD<br>CNS Clinical Trials<br>108 NE 1st St.<br>Fort Lauderdale, FL 33301 | |
| 1105 | 2 | Daniel H. Brune, MD<br>nTouch Research Corporation<br>222 NE Monroe, Suite 904<br>Peoria, IL 61602 | |
| 1105 | 3 | Lisa M. Cohen, DO<br>Suncoast Clinical Research, Inc.<br>5340 Gulf Drive, Suite 203<br>New Port Richey, FL 34652 | |
| 1105 | 4 | Steven K. Elliott, MD<br>MediSphere Medical Research Center, LLC<br>2345 W. Franklin St. Suite 202<br>Evansville, IN 47712 | |
| 1105 | 5 | William Travis Ellison, MD<br>Radiant Research<br>552-A Memorial Drive, Ext.<br>Greer, SC 29651 | |
| 1105 | 6 | Thomas Fiel, MD<br>Tempe Primary Care Associates<br>5030 South Mill Avenue D-12<br>Tempe, AZ 85282 | |
| 1105 | 14 | David L. Fried, MD<br>Omega Medical Research<br>400 Bald Hill Road<br>Warwick, RI 02886 | |

## List of Investigators Sorted by Study Number

| Study No. | Site No. | Principal Investigator | Sub-Investigators |
|---|---|---|---|
| 1105 | 7 | W. Thomas Garland, MD<br>Radiant Research – Lawrenceville<br>3100 Princeton Pike<br>Bldg. 1, Third Floor<br>Lawrenceville, NJ 08648 | [redacted] |
| 1105 | 31 | Harry J. Geisberg, MD<br>Radiant Research<br>1657 East Greenville Street<br>Anderson, SC 29621 | [redacted] |
| 1105 | 8 | Larry I Gilderman, DO<br>University Clinical Research, Inc.<br>1150 N. University Drive<br>Pembroke Pines, FL 33024 | [redacted] |
| 1105 | 9 | David Hassman, DO<br>Comprehensive Clinical Research<br>160 S. White Horse Pike – 2nd Floor<br>Berlin, NJ 08009 | [redacted] |
| 1105 | 10 | Kim T. Heaton, MD<br>Advanced Clinical Research<br>34 south 500 East, Suite 102<br>Salt Lake City, UT 84102 | [redacted] |
| 1105 | 20 | Carlos Omar Hernandez, MD<br>WellMed at Northwest 410<br>4600 N.W. Loop 410, Suite 110<br>San Antonio, TX 78229 | [redacted] |
| 1105 | 11 | Marvin A. Heuer, MD<br>925 NW 56th Terrace, suite B<br>Gainesville, FL 32605 | [redacted] |
| 1105 | 12 | Peter R. Honig, DO<br>Honig Family Medicine<br>1805 S. Broad Street<br>Philadelphia, PA 19148 | [redacted] |
| 1105 | 13 | Rodney K. Ison, MD<br>Community Health Care<br>944 E. cherry Street<br>Canal Fulton, OH 44614 | [redacted] |
| 1105 | 35 | Murray A. Kimmel, DO<br>Comprehensive NeuroScience, Inc. 2295 W. Eau Gallie Blvd., Suite B<br>Melbourne, FL 32935 | [redacted] |

## List of Investigators Sorted by Study Number

| Study No. | Site No. | Principal Investigator | Sub-Investigators |
|---|---|---|---|
| 1105 | 15 | Joseph B. Liddle, MD<br>Advanced Clinical Research34 South 500 East, Suite 102<br>Salt Lake City, UT 84102 | [redacted] |
| 1105 | 16 | Terry Little, MD<br>Advanced Clinical Research<br>1074 N. Cole Road<br>Boise, ID 83704 | [redacted] |
| 1105 | 17 | Antoinette Mangione, MD, PharmD<br>Radiant Research<br>9880 Bustleton Avenue, Suite 203<br>Philadelphia, PA 19115 | [redacted] |
| 1105 | 33 | Richard Allen Margolin, DO<br>MPC- Homewood/Glenwood<br>17450 South Halsted Street<br>Homewood, IL 60430 | [redacted] |
| 1105 | 19 | Manoj Patel, MD<br>3660 Arlington, Avenue<br>Riverside, CA 92506 | [redacted] |
| 1105 | 21 | Mark K. Radbill, DO<br>Neshaminy Medical, PC<br>2426 Bristol Road<br>Bensalem, PA 19020 | [redacted] |
| 1105 | 22 | Lee P. Ralph, MD<br>6699 Alvarado Road, Suite 2100<br>San Diego, CA 92120 | [redacted] |
| 1105 | 24 | Gary E. Ruoff, MD<br>Westside Family Medical Center, PC<br>6565 West Main Street<br>Kalamazoo, MI 49009 | [redacted] |
| 1105 | 25 | Morris Scherlis, MD<br>Center for Pain Management<br>927 Franklin St. 2nd Floor<br>Huntsville, AL 35801 | [redacted] |

## List of Investigators Sorted by Study Number

| Study No. | Site No. | Principal Investigator | Sub-Investigators |
|---|---|---|---|
| 1105 | 32 | James J. Schulte, MD<br>Community Health Care, Inc.<br>Norton Family Practice<br>1193 Norton Ave., Suite A<br>Norton, OH 44203 | [redacted] |
| 1105 | 26 | Philip A. Snell, MD<br>406 Memorial Drive Ext.<br>Greer, SC 29651 | [redacted] |
| 1105 | 27 | Timothy S. Truitt, MD<br>nTouch Research Corporation<br>2202 S. Babcock Street, Suite 104<br>Melbourne, FL 32901 | [redacted] |
| 1105 | 28 | Ralph Wade, DO<br>Advanced Clinical Research<br>34 South 500 East, Suite 102<br>Salt Lake City, UT 84102 | [redacted] |
| 1105 | 29 | Arnold J. Weil, MD<br>nTouch Research<br>1431 White Circle<br>Marietta, GA 30066 | [redacted] |
| 1105 | 30 | David L. Williams, MD<br>Atlantic Institute of Clinical Research<br>350 N. Clyde Morris Blvd.<br>Daytona Beach, FL 32114 | [redacted] |
| 1106 | 9 | Thomas M. Adams, MD<br>Primary Care Research<br>300 South 8th Street Suite 480W<br>Murray, KY 42071 | [redacted] |
| 1106 | 1 | Lawrence K. Alwine, DO<br>Brandywine Clinical Research<br>77 Manor Ave., Suite 100<br>Downingtown, PA 19335 | [redacted] |
| 1106 | 2 | John D. Angeloni, DO<br>City Line Family Medicine<br>301 City Line Avenue, Suite 100<br>Bala Cynwyd,, PA 19004 | [redacted] |

## List of Investigators Sorted by Study Number

| Study No. | Site No. | Principal Investigator | Sub-Investigators |
|---|---|---|---|
| 1106 | 4 | Robert B. Bettis, MD<br>Edmonds Family Medicine Clinic<br>7315 212th Street S.W. Suite 101<br>Edmonds, WA 98026 | |
| 1106 | 5 | Brian Thomas Bock, DO<br>Harleysville Medical Associates<br>176 Main Street<br>Harleysville, PA 19438 | |
| 1106 | 6 | Thomas J. Boud, MD<br>Advanced Clinical Research<br>34 South 500 East, Suite 102<br>Salt Lake City, UT 84102 | |

## List of Investigators Sorted by Study Number

| Study No. | Site No. | Principal Investigator | Sub-Investigators |
|---|---|---|---|
| 1106 | 33 | James J. Brown, MD<br>Community Health Care Barberton<br>Community Health Care, Inc.<br>290 9th Street, NE<br>Barberton, OH 44203 | [redacted] |
| 1106 | 7 | Nancy G. Campbell, MD<br>Breco Research, Ltd.<br>902 Frostwood, Suite 223<br>Houston TX 77024 | [redacted] |
| 1106 | 8 | David Carter, MD<br>Radiant Research-Austin<br>12221 MoPac Expressway North<br>Austin, TX 78758 | [redacted] |
| 1106 | 34 | John Champlin, MD<br>6651 Madison Avenue<br>Carmichael, CA 95608 | [redacted] |
| 1106 | 11 | David Damian Jr, MD<br>DiscoveResearch, Inc.<br>2210 East 29th Street<br>Bryan, TX 77802 | [redacted] |
| 1106 | 35 | R. David Ferrera, MD<br>107 Scripps Dr., Suite 210<br>Sacramento, CA 95825 | [redacted] |
| 1106 | 31 | Timothy J. Fiorillo, DO<br>Perkiomen Valley Family Practice<br>78 Second Avenue<br>Collegeville, PA 19426 | [redacted] |
| 1106 | 42 | Harry I. Geisberg, MD<br>Radiant Research, Inc.<br>1657 East Greenville Street<br>Anderson, SC 29621 | [redacted] |
| 1106 | 38 | Larry I. Gilderman, DO<br>University Clinical Research, Inc.<br>1150 N. University Drive<br>Pembroke Pines, FL 33024 | [redacted] |
| 1106 | 15 | James A. Gray, MD<br>Parkway Medical Group, PC<br>108 Medical Center Blvd., Suite G50<br>Fayetteville, TN 37334 | [redacted] |
| 1106 | 39 | David R. Hassman, DO<br>Comprehensive Clinical Research<br>160 S. White Horse Pike – 2nd Floor<br>Berlin, NJ 08009 | [redacted] |
| 1106 | 41 | Rodney K. Ison, MD<br>Community Health Care<br>944 E. Cherry Street<br>Canal Fulton, OH 44614 | [redacted] |

## List of Investigators Sorted by Study Number

| Study No. | Site No. | Principal Investigator | Sub-Investigators |
|---|---|---|---|
| 1106 | 17 | James D. King, MD<br>Prime Care Medical Center<br>One Prime Care Drive<br>Selmer, TN 38375 | |
| 1106 | 36 | Martha J. Klipec, MD<br>Hartville Family Physicians<br>855 W. Maple, Suite 110<br>Hartville, OH 44632 | |
| 1106 | 19 | David Mansfield, MD<br>DiscoveResearch, Inc.<br>3420 Fannin, Suite 175<br>Beaumont, TX 77701 | |
| 1106 | 13 | Randle T. Middleton, MD<br>Greater Huntsville Family Practice, PC<br>4769 Whitesburg Dr., Suite 202<br>Huntsville, AL 35802 | |
| 1106 | 32 | Kenneth Alan Morris, DO<br>Bensalem Medical Practice<br>2373 Pasqualone Blvd.<br>Bensalem, PA 19020 | |
| 1106 | 20 | Julio E. Navarro, MD, F.A.A.F.P.<br>Glasgow Family Practice<br>2600 Glasgow Avenue, Suite 120<br>Newark, DE 19702 | |
| 1106 | 21 | Michael J. Noss, MD<br>Radiant Research<br>7720 Montgomery Road<br>Cincinnati, OH 45236 | |
| 1106 | 22 | John E. Pappas, MD<br>Central Kentucky Research Associates, Inc.<br>2801 Palumbo Drive, Suite 200<br>Lexington, KY 40509 | |

## List of Investigators Sorted by Study Number

| Study No. | Site No. | Principal Investigator | Sub-Investigators |
|---|---|---|---|
| 1106 | 23 | Gary P. Plundo, DO<br>nTouch Research Corporation<br>9550 West 167th Street<br>Orland Park, IL 60462 | |
| 1106 | 24 | Bryan C. Pogue, MD<br>Radiant Research Boise<br>6565 W. Emerald Street<br>Boise, ID 83704 | |
| 1106 | 22 | Lee P. Ralph, MD<br>San Diego Sports Medicine and Family Health Center<br>6699 Alvarado Road, Suite 2100<br>San Diego, CA 92120 | |
| 1106 | 16 | Kenneth W. Rictor, MD<br>William J. Keating, MD (former PI)<br>SFM Clinical Trials, PC<br>3730 Scotland Road<br>Scotland, PA 17254 | |
| 1106 | 25 | Gerald R. Shockey, MD<br>Clinical Research Advantage, Inc.<br>Desert Clinical Research, LLC<br>606 North Country Club Drive, Suite 5<br>Mesa, AZ 85201 | |
| 1106 | 26 | Ronald Keith Stegemoller, MD<br>American Health Network<br>5250 East US 36, Suite 610<br>Avon, IN 46123 | |
| 1106 | 37 | David L. Williams, MD<br>Atlantic Institute of Clinical Research<br>350 N. Clyde Morris Blvd.<br>Daytona Beach, FL 32114 | |
| 1106 | 27 | Julius Wolfram, MD<br>Research Across America<br>RHD Professional Plaza 4<br>9 Medical Parkway, Suite 202<br>Dallas, TX 75234 | |
| 1106 | 28 | James P. Wymer, MD, PhD<br>Upstate Clinical Research, LLC<br>3 Atrium Drive, Suite 250<br>Albany, NY 12205 | |

## List of Investigators Sorted by Study Number

| Study No. | Site No. | Principal Investigator | Sub-Investigators |
|---|---|---|---|
| 1106 | 29 | Douglas G. Young, MD<br>Northern California Research Corp.<br>7529 Sunset Avenue, Suite C-1<br>Fair Oaks, CA 95628 | [redacted] |
| 1107 | 1 | Maria Josefa Gutierrez, MD<br>CNS Clinical Trials<br>108 NE 1st St.<br>Fort Lauderdale, FL 33301 | |

# ACTION PACKAGE CHECKLIST

| Application Information | | | |
|---|---|---|---|
| BLA #<br>NDA # 21-777 | BLA STN#<br>NDA Supplement # | If NDA, Efficacy Supplement Type | |
| Proprietary Name: Amrix Extended-Release Capsule 15 and 30 mg<br>Established Name: cyclobenzaprine hydrochloride<br>Dosage Form: Capsule | | Applicant: ECR Pharmaceuticals | |
| RPM: Lisa Malandro | | Division: DAARP | Phone # 301-796-1251 |

| NDAs: | 505(b)(2) NDAs and 505(b)(2) NDA supplements: |
|---|---|
| NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)<br>Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)<br><br>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) | Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):<br><br>Flexeril<br><br>Provide a brief explanation of how this product is different from the listed drug.<br>It is an extended-release formulation<br><br>☐ If no listed drug, check here and explain:<br><br>**Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.**<br><br>☒ Confirmed ☐ Corrected<br>Date: January 31, 2007 |

| | |
|---|---|
| ❖ User Fee Goal Date<br>❖ Action Goal Date (if different) | 2/7/07<br>2/2/07 |
| ❖ Actions | |
| • Proposed action | ☒ AP ☐ TA ☐ AE<br>☐ NA ☐ CR |
| • Previous actions *(specify type and date for each action taken)* | ☐ None<br>Approvable 2/28/05 |
| ❖ Advertising *(approvals only)*<br>Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)* | ☒ Requested in AP letter<br>☐ Received and reviewed |

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 3S; muscle relaxant

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

| ❖ Application Integrity Policy (AIP) | |
|---|---|
| • Applicant is on the AIP | ☐ Yes ☒ No |
| • This application is on the AIP | ☐ Yes ☒ No |
| • Exception for review *(file Center Director's memo in* Administrative Documents *section)* | ☐ Yes ☐ No |
| • OC clearance for approval *(file communication in* Administrative Documents *section)* | ☐ Yes ☐ Not an AP action |
| ❖ Public communications (approvals only) | |
| • Office of Executive Programs (OEP) liaison has been notified of action | ☒ Yes ☐ No |
| • Press Office notified of action | ☒ Yes ☐ No |
| • Indicate what types (if any) of information dissemination are anticipated | ☒ None<br>☐ FDA Press Release<br>☐ FDA Talk Paper<br>☐ CDER Q&As<br>☐ Other |

| | |
|---|---|
| ❖ Exclusivity | |
| • NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)* | ☒ Included |
| • Is approval of this application blocked by any type of exclusivity? | ☒ No ☐ Yes |
| • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.* | ☒ No ☐ Yes<br>If, yes, NDA/BLA # and date exclusivity expires: |
| • NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☒ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☒ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☒ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| ❖ Patent Information (NDAs and NDA supplements only) | |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | ☒ Verified<br>☐ Not applicable because drug is an old antibiotic. |
| • Patent Certification [505(b)(2) applications]:<br>Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(*i*)(A)<br>☒ Verified<br><br>21 CFR 314.50(i)(1)<br>☐ (ii) ☐ (iii) |
| • [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | ☒ No paragraph III certification<br>Date patent will expire |
| • [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).* | ☒ N/A (no paragraph IV certification)<br>☐ Verified |
| • [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.<br><br>Answer the following questions for **each** paragraph IV certification:<br><br>(1) Have 45 days passed since the patent owner's receipt of the applicant's | ☐ Yes ☐ No |

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

| | |
|---|---|
| within the 45-day period).<br><br>*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*<br><br>*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.* | |
| **Summary Reviews** | |
| ❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)* | 2/2/07<br>2/28/05 |
| ❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)* | |
| **Labeling** | |
| ❖ Package Insert | |
| • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) | 2/7/07 |
| • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) | 1/25/07 |
| • Original applicant-proposed labeling<br>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable | 4/29/04 |
| ❖ Patient Package Insert | |
| • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) | |
| • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) | |
| • Original applicant-proposed labeling | |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable | |
| ❖ Medication Guide | |
| • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) | |
| • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) | |
| • Original applicant-proposed labeling | |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | |
| ❖ Labels (**full color** carton and immediate-container labels) | |
| • Most-recent division-proposed labels (only if generated after latest applicant submission) | NA |
| • Most recent applicant-proposed labeling | 1/25/07 |
| ❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)* | ☒ DMETS 9/13/04, 12/28/06<br>☐ DSRCS<br>☒ DDMAC 10/25/04<br>☐ SEALD<br>☐ Other reviews<br>☐ Memos of Mtgs |

| Administrative Documents | |
|---|---|
| ❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)* | L Malandro (revised) 1/17/07<br>P Balcer 11/22/04 |
| ❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)* | ☒ Included |
| ❖ AIP-related documents<br>• Center Director's Exception for Review memo<br>• If AP: OC clearance for approval | |
| ❖ Pediatric Page (all actions) | ☒ Included |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)* | ☒ Verified, statement is acceptable |
| ❖ Postmarketing Commitment Studies | ☒ None |
| • Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)* | |
| • Incoming submission documenting commitment | |
| ❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons) | Included |
| ❖ Internal memoranda, telecons, email, etc. | Included |
| ❖ Minutes of Meetings | |
| • Pre-Approval Safety Conference *(indicate date; approvals only)* | 1/8/07 |
| • Pre-NDA/BLA meeting *(indicate date)* | ☐ No mtg 5/28/03 |
| • EOP2 meeting *(indicate date)* | ☐ No mtg 12/13/01 |
| • Other (e.g., EOP2a, CMC pilot programs) | |
| ❖ Advisory Committee Meeting | ☒ No AC meeting |
| • Date of Meeting | |
| • 48-hour alert or minutes, if available | |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) | |

| CMC/Product Quality Information | |
|---|---|
| ❖ CMC/Product review(s) *(indicate date for each review)* | 2/17/05, 1/29/07 |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)* | ☒ None |
| ❖ BLAs: Product subject to lot release (APs only) | ☐ Yes ☐ No |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| • ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)* | 1/29/07 |
| • ☐ Review & FONSI *(indicate date of review)* | |
| • ☐ Review & Environmental Impact Statement *(indicate date of each review)* | |
| ❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)* | ☒ Not a parenteral product |
| ❖ Facilities Review/Inspection | |
| ❖ NDAs: Facilities inspections (include EER printout) | Date completed: 10/18/06<br>☒ Acceptable<br>☐ Withhold recommendation |

| | |
|---|---|
| ❖ BLAs: Facility-Related Documents<br>• Facility review *(indicate date(s))*<br>• Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)* | ☐ Requested<br>☐ Accepted<br>☐ Hold |
| ❖ NDAs: Methods Validation | ☐ Completed<br>☐ Requested<br>☐ Not yet requested<br>☒ Not needed |
| **Nonclinical Information** | |
| ❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | 2/9/05 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)* | ☒ None |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | ☒ No carc |
| ❖ ECAC/CAC report/memo of meeting | |
| ❖ Nonclinical inspection review Summary (DSI) | ☒ None requested |
| **Clinical Information** | |
| ❖ Clinical review(s) *(indicate date for each review)* | 2/28/05, 1/25/07 |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review | 2/28/05 |
| ❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)* | ☒ None |
| ❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)* | ☒ Not needed |
| ❖ Safety Update review(s) *(indicate location/date if incorporated into another review)* | 2/28/05 |
| ❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)* | NA |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)* | ☒ Not needed |
| ❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)* | ☐ None requested |
| • Clinical Studies | |
| • Bioequivalence Studies | |
| • Clin Pharm Studies | 10/27/05 |
| ❖ Statistical Review(s) *(indicate date for each review)* | ☒ None |
| ❖ Clinical Pharmacology review(s) *(indicate date for each review)* | ☐ None 2/22/05, 1/26/07 |

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.

(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.

(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).

(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.

(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).

(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.

(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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/s/

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Lisa Malandro
2/8/2007 03:52:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-777

**DISCIPLINE REVIEW LETTER**

ECR Pharmaceuticals
404 Saw Mill Road
East Berne, NY 12059

Attention: Robert G. Ferraino
Regulatory Affairs

Dear Mr. Ferraino:

Please refer to your new drug application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for AMRIX (cyclobenzaprine hydrochloride extended-release capsules).

We also refer to your submissions dated September 19 and November 22, 2006.

The Division of Medication Errors and Technical Support (DMETS) has completed its review and they have identified the following deficiencies:

1. **DESCRIPTION** section of the package insert:

   a. The nonproprietary name should be displayed as "cyclobenzaprine hydrochloride extended-release capsules." Therefore, replace "HCl" in the nonproprietary name with "hydrochloride" and add a hyphen between "extended" and "release."

   b. Provide pharmacological/ therapeutic class in the "description" section as required in 21CFR 201.57(a)(v).

   c. List the inactive ingredients in alphabetical order (see USP <1091> Labeling of Inactive Ingredients).

2. **HOW SUPPLIED** section of the package insert:

   a. Replace "AMRIX modified release capsules" with "AMRIX extended-release capsules."

   b. Revise the storage temperature statement to the following:

      Store at 25°C (77°F); excursions permitted to 15-30°C (59-86 °F)
      [see USP Controlled Room Temperature]

3. Immediate container labels (bottle of 60)

   a. Revise the presentation of the proprietary name, established name, and strength as follows, ensuring the prominence of the established name at least half as that of the proprietary name. Note that the prominence is an overall effect of the font size, shape, and boldness, etc.

      Amrix
      (Cyclobenzaprine Hydrochloride Extended-release Capsules)
      15 mg

   b. Relocate the statement "Each Extended Release Capsule Contains: Cyclobenzaprine HCl…15 mg" to the side panel.

   c. Delete the ' [redacted] ' from the principal display panel as the "Usual Dosage" already appears on the side label.

   d. Revise the storage temperature statement as recommended in 2(b) above or, if space is limited, either of the following:

      Store at 25°C (77 °F); excursions 15-30°C (59-86 °F)
      Store at 25°C (77°F) (see insert)

4. Blister labeling:

   Provide mock-up labeling for individual blisters and blister cards. See comment 3(a) above for the presentation of the proprietary name, nonproprietary name, and strength.

5. Carton labels for bottles:

   Submit mock-up labeling for the corrugated carton for bottles. The labeling should be in color and in the same size as that proposed for marketing. In addition to the information provided on page 42 of the 9/19/06 amendment, provide the following:

   a. Revise the presentation of the proprietary name, established name and strength as stated above for container labels. See comments 1 through 4 under Container Label.

   b. "Rx only" should be displayed prominently on the main panel.

   c. Include NDC number, storage condition, and bar code.

   d. Include statements such as "See package insert for dosage information" and "Keep out of reach of children."

6. Carton labeling for professional samples:

   a. See Container Label comments 1 through 4.

   b. The color configuration of black print on the dark-color background of the professional sample bin is difficult to read and may be confusing. Revise accordingly for both the strengths.

   c. Retain "Rx Only" statement and delete '[redacted] from the label.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 796-1251.

Sincerely,

*{See appended electronic signature page}*

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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## Basham, Lisa

**To:** Robert G. Ferraino
**ubject:** CMC request/NDA 21-777

Hi, Robert!

Below is a request from the CMC reviewer pertaining to your NDA. Please respond as soon as possible. Feel free to give me a call with any questions!

1. Please confirm that the facilities for manufacturing and control of the drug substance and drug product remain unchanged from the original NDA submission. Please provide name, address, and registration number of the facilities as required for FDA Form 356h under "Establishment Information."

2. Provide updated stability data for the drug product.

3. Provide updated mock-up container and carton labels. These labels should be presented in size and color as proposed for marketing.

Thanks!

***Lisa Basham, MS***
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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/s/

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Lisa Basham-Cruz
9/11/2006 10:32:37 AM
CSO

**Basham, Lisa**

**From:** Basham, Lisa
**Sent:** Wednesday, October 04, 2006 3:47 PM
**To:** 'Robert G. Ferraino'
**Subject:** 10-4-06 CMC request

Bob,,

Due to the potential for dose-dumping of controlled-release formulations in the presence of alcohol, we need you to provide the following information about your product.

Provide data on in vitro drug release using the test procedure described in the NDA but with the media containing varying amounts of ethyl alcohol. Choose the media containing 0, 4, 20, and 40 % alcohol and the time points sufficient to cover the entire release profile from initial time to the time when asymptote is reached.

Alternatively, provide a rationale that in the setting of ingesting alcohol, any resultant rapid release of cyclobenzaprine from this modified-release formulation would not result in a serious adverse event.

Please submit this information as soon as it is available. Feel free to give me a call with any questions.

Regards,

***Lisa Basham, MS***
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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/s/

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Lisa Basham-Cruz
10/12/2006 12:27:28 PM
CSO

## Basham, Lisa

**From:** Basham, Lisa
**ent:** Monday, October 02, 2006 3:12 PM
**To:** 'Robert G. Ferraino'
**Subject:** 10-2-06 facilities question #2

Bob,

Your 9/19/06 amendment lists [redacted] for the manufacture of the drug substance. However, the original NDA stated that [redacted] was the drug substance manufacturer for the clinical batches. The drug substance for the manufacture of the commercial drug product will be supplied by [redacted].

Please clarify that [redacted] is no longer the supplier of the drug substance and [redacted] will be the only drug substance supplier for commercial drug product.

Regards,

***Lisa Basham, MS***
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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**Basham, Lisa**

**From:** Basham, Lisa
**Sent:** Monday, October 02, 2006 10:56 AM
**To:** 'Robert G. Ferraino'
**Subject:** Urgent question re [redacted]

Bob, Our facilities inspection team has received information that the [redacted], is no longer in business. Please provide clarification/explanation ASAP.

Thanks!

*Lisa Basham, MS*
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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**From:** Robert G. Ferraino [mailto [redacted]
**Sent:** Wednesday, September 20, 2006 11:00 AM
**To:** Basham, Lisa
**Subject:** September 11 Request for Chemistry Information

Hi Lisa,

I sent our written response to the Chemistry Reviewer's request for information (requested on September 11, 2006) to the Central Document Room (Ammendale Road) by FedEx courier yesterday. The submission will be delivered this morning. The submission contained one archival copy and two review copies. Attached, please find a copy of the Cover Letter for your reference.

Regards,

Robert G. Ferraino
Regulatory Affairs
Telephone: [redacted]
Fax: [redacted]
E-mail: [redacted]

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/s/

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Lisa Basham-Cruz
10/12/2006 12:24:26 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: January 14, 2005

From: Renan A. Bonnel, Pharm.D., MPH
Division of Drug Risk Evaluation, HFD- 430

Through: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

To: Brian Harvey, M.D., Ph.D., Acting Director
Division of Antiinflammatory, Analgesics and Ophthalmic Drug Products (DAAODP), HFD-550

Subject: A review of serious adverse events reported in association with the use of cyclobenzaprine (Flexeril; NDA 21-070)

**Confidential: Contains IMS data; not to be used outside of the FDA without clearance from IMS.**

## EXECUTIVE SUMMARY

This memo is in response to Dr. Christina Fang's (HFD-550) recent request to provide a review update of the serious postmarketing adverse event reports associated with the use of cyclobenzaprine. On July 14, 1999, Kathleen Bennett and Kate Phelan from the Office of Drug Safety (ODS, formerly OPDRA) completed a *qualitative* review of serious adverse events with cyclobenzaprine use. Their review noted that accidental and deliberate overdoses were frequently reported with cyclobenzaprine. Given the short turn around time for the latest request, ODS agreed to provide *quantitative* information including crude counts of all serious adverse event reports with particular attention to cardiac, hepatobiliary and seizure events, demographic data of all adverse events, a recent literature review and a detailed review of death reports that are unrelated to drug overdoses since the last review in 1999. We did not attempt to match duplicate reports or perform individual case reviews of all adverse event reports. Since individual reviews of all reports was not conducted, the information related to dose, duration, onset, history of drug abuse, and the causality could not be assessed.

A total of 438 serious adverse events for cyclobenzaprine were identified in the Adverse Event Reporting System (AERS) between 6/18/1999 and 12/17/2004. There were 190 females, 175 males, and the gender was unknown in 73 reports. There were 417 US and 9 foreign reports. The most commonly reported adverse event terms were completed suicide, intentional overdose, and multiple drug overdoses involving co-ingestion of other medications including narcotics, TCAs, SSRIs, alcohol, narcotics and benzodiazepines.

The outcomes included hospitalization (134), disability (14), life-threatening (15), intervention required (23), and deaths (235).

Of 235 death reports, only five fatalities were unrelated to known drug overdoses. There were two females and three males aged 20, 48, 52, 64, and 81 years who experienced seizure/arrhythmia (1), acute respiratory distress syndrome (1), severe hypoglycemia (1), respiratory arrest (1), or multiple organ failure (1) while receiving cyclobenzaprine. Four cases were confounded by underlying serious medical illnesses (malignancy, diabetes mellitus, alcoholism or biliary cirrhosis), and/or the use of multiple co-suspect medications (multiple chemotherapeutic agents, tramadol) that might have contributed to the events and the fatal outcome. The fifth case provided very limited information. The causal role of cyclobenzaprine in all cases could not be determined.

An overview of AERS crude counts and particularly cardiac, hepatobiliary and seizure adverse event terms did not provide any new information since the last ODS review (1999). Tachycardia, dyspnea, cardiac arrest, arrhythmia, hypotension, pulmonary edema, hepatobiliary dysfunction, and seizures have been reviewed previously and continue to occur in postmarketing reports. It is noteworthy that multiple adverse event terms related to intentional overdose were frequently mentioned in cardiac, hepatobilary and seizure reports. Literature searches did not provide additional information.

Cyclobenzaprine use has increased slightly over the last five years with [redacted] prescriptions dispensed in 1999 and [redacted] dispensed in 2003.

In summary, completed suicide and drug overdoses are the most frequently reported serious adverse event terms with cyclobenzaprine between 6/18/1999 and 12/17/2004 in the FDA's AERS database. These findings concur with the findings of the 1999 ODS review.

## I. DRUG USE

Over [redacted] prescriptions of cyclobenzaprine (Flexeril®) tablets have been dispensed by retail pharmacies in the U.S since 1998. The following table summarizes the projected total prescriptions of cyclobenzaprine dispensed by retail pharmacies (chain, independent, food store, and mail order) in the U.S from 1998 until November 2004. The use information listed below for cyclobenzaprine is not complete, since the drug was approved in August 1977.

**This information is not to be used outside of the FDA without prior clearance by IMS Health.**

| Drug | 2004 (Jan-Nov) | 2003 (Total) | 2002 (Total) | 2001 (Total) | 2000 (Total) | 1999 (Total) | 1998 (Total) |
|---|---|---|---|---|---|---|---|
| Flexeril | [redacted] | | | | | | |

**(in thousands; ADD THREE 000's TO EACH FIGURE)**

## II. LITERATURE REVIEW: [1,2,3]

On December 17, 2004, the Medline database was searched from 1999 through the present using the search term " cyclobenzaprine or Flexeril". Eighteen references were retrieved. Three references discussed adverse events related to cyclobenzaprine use. One case[2] involved psychosis following cyclobenzaprine use, the second case[3] reported hallucinations in an elderly patient taking recommended doses of cyclobenzaprine and the third[4] case was drowning due to cyclobenzaprine and ethanol use. Psychosis, hallucinations, and cyclobenzaprine-alcohol drug interaction are mentioned in the product labeling.

## III. OVERVIEW OF THE SERIOUS ADVERSE EVENTS

Between June 30, 1999 and December 15, 2004, there were 438 adverse event reports with serious outcomes associated with cyclobenzaprine in AERS. The 20 most commonly reported events were as follows (a report may contain more than one adverse event term):

| | | | |
|---|---|---|---|
| Completed Suicide | 81 | Cardiac Arrest | 20 |
| Multiple Drug Overdose | 57 | Toxicologic Test Abnormal | 20 |
| Intentional Drug Overdose | 46 | Heart Rate Increased | 19 |
| Coma | 44 | Drug Screen Positive | 18 |
| Overdose | 42 | Convulsion | 17 |
| Accidental Overdose | 38 | Loss of Consciousness | 17 |
| Cardio-Pulmonary Arrest | 26 | Agitation | 16 |
| Drug Toxicity | 26 | Hallucination | 16 |
| Drug Interaction | 22 | Medication Error | 16 |
| Hypotension | 21 | Vomiting | 16 |

It is interesting to note that completed suicide and intentional and multiple drug overdoses were the most frequently reported adverse event terms.

The reported demographics included 4 children (< 17 years); 336 adults (17 to 60 years), and 53 elderly adults (> 61 years). There were 190 females and 175 males. Age and gender were not provided in 45 and 73 cases, respectively. There were 417 US and 9 foreign reports. The outcomes included hospitalization (134), disability (14), life-threatening (15), intervention required (23), and deaths (235).

## IV. FATALITIES/OVERDOSES

Between June 30, 1999 and December 17, 2004, there were 235 death reports (crude counts) for cyclobenzaprine in AERS. The majority of the reports were domestic (226) and received from health care professionals. The ages ranged from 15 to 95 years old. There were 90 females, 82 males and the gender was unknown in 63 reports. Two hundred thirty (230) reports involved drug overdoses mostly involving coingestion of multiple medications including narcotics, TCAs, SSRIs, alcohol, narcotics and benzodiazepines.

The remaining five death reports appeared to be unrelated to drug overdoses. There were two females and three males aged 20, 48, 52, 64, and 81 years who experienced seizure/arrhythmia (1), acute respiratory distress syndrome (1), severe hypoglycemia (1), respiratory arrest (1), or multiple organ failure (1) while receiving cyclobenzaprine. Four cases were confounded by underlying serious medical illnesses (malignancy, diabetes mellitus, alcoholism or biliary cirrhosis), and/or the use of multiple co-suspect medications (multiple chemotherapeutic agents, tramadol) that might have contributed to the events and the fatal outcome. The fifth case provided very limited information. The causal role of cyclobenzaprine in all cases could not be determined.

A narrative of each case is presented below:

**FDA 3458028-4, 2000, USA, HCP**
A 48 year-old female received cyclobenzaprine 10mg three times daily as needed for chronic hip pain secondary to bilateral hip replacement. The patient developed hyperbilirubinemia (5-7 mg/dl), with normal prothrombin time, and elevated AST and ALT (in the range of 200 U/ml) 6 months or 1-1 1/2 years (from two different sources) after starting cyclobenzaprine therapy. The liver changes were thought to be consistent with either autoimmune hepatitis or primary biliary cirrhosis by gastroenterologist. The liver biopsy was suggestive of primary biliary cirrhosis. Multiple blood cultures were negative. Despite close monitoring, the patient developed hepatorenal syndrome, ascites, hepatic coma, acute respiratory failure, GI bleed, acute renal failure and died. The reporter stated that the events were possible related to biliary cirrhosis or drug-induced toxic hepatitis. Her medical history was significant for avascular necrosis of right hip, hypertension, fluid retention, osteoarthritis, and allery to Motrin and Clinoril. Concomitant medications included Hytrin, Darvocet and Lasix.

**FDA 3966238-2, 2002, USA, Consumer**
A 20 year old male died of "respiratory arrest" after taking Xanax, Flexeril and "Vicopren" for severe back pain following a minor motor vehicle accident. The dosages and duration of therapy were not reported. The reporter stated that all medications were within "therapeutic limits". An autopsy revealed no evidence of illicit drug use. The overall available information on this consumer case was very limited for a meaningful medical assessment of drug-event causal association.

**FDA 4048559-0, 2003, USA, HCP**
An 81 year-old male with a history of Parkinson's disease, diabetes mellitus, CHF, renal failure, recurrent DVT, pulmonary embolism, GI bleed and atrial fibrillation developed severe hypoglycemia (blood glucose: 6 mg/dl) and died after taking 2 doses of 10 mg cyclobenzaprine. The patient's most recent baseline blood glucose levels were 155/81/93 mg/dl. At the time of the event, the patient was receiving twenty other medications including glipizide 5 mg daily. The reporter (HCP) suggested cyclobenzaprine as a suspect medication. No further information was available.

**FDA 4220263-5, 2003, USA, HCP**
A 64 year-old female with a history of lymphoma died of adult respiratory distress syndrome one day after receiving chemotherapy with Rituxan (rituximab, investigational), cyclophosphomide, doxoribucin, vincrisitine and prednisone. The patient was also taking Neulasta (pegfilgrastim) and multiple pain medications. The physician reported that there was a reasonable probability that

the death may have been caused by Neulasta. However, propoxyphene with acetaminophen, cyclobenzaprine and Lortab were listed as co-suspect medications. The autopsy revealed focal pulmonary consolidation, cardiomegaly with minimal artherosclerosis without evidence of thrombi, hepatomegaly, and pulmonary congestion. No further details were available.

**FDA 3532551-6, 2000, USA, Consumer**
A 52-year old male died following seizure and cardiac arrhythmia while receiving tramadol and cyclobenzaprine concomitantly for back pain associated with surgery. This was the patient's second seizure episode after starting the combination therapy 6 months ago. The patient had no history of cardiac or seizure disorders. His medical history was significant for smoking, asthma, alcoholism and drug addiction (recovering). At the time of death, there were no illegal drugs or alcohol detected in his blood. Cyclobenzaprine (structurally related to tricyclic antidepressants) may enhance the seizure risk in patients taking tramadol according to product labeling.

## V. OVERVIEW OF SELECTED ADVERSE EVENTS BY BODY SYSTEM

### A. CARDIOVASCULAR SYSTEM

*Labeling*[4]
The following are included in the labeling in the *Adverse Reactions* section:
Incidence less than 1 in 100—tachycardia, arrhythmia, vasodilation, palpitation, and hypotension.
Causal relationship unknown—reported rarely: hypertension, myocardial infarction, heart block, and stroke.

*AERS*
The AERS database was searched for Flexeril (cyclobenzaprine) cardiac adverse event reports that were received between June 18, 1999 and December 17, 2004, using the MedDRA term, cardiac disorders (SOC). AERS contained 155 reports (crude counts) associated with the use of cyclobenzaprine. The 20 most commonly reported adverse event terms are as follows (a report may contain more than one adverse event term):

| | | | |
|---|---|---|---|
| Cardio-Respiratory Arrest | 26 | **Toxicologic Test Abnormal** | 11 |
| **Completed Suicide** | 24 | Cardiomegaly | 10 |
| Coma | 21 | Loss of Consciousness | 10 |
| Cardiac Arrest | 20 | Arrhythmia | 9 |
| **Overdose** | 16 | Hypotension | 9 |
| **Multiple Drug Overdose** | 15 | **Intentional Overdose** | 9 |
| **Drug Toxicity** | 15 | Acidosis | 8 |
| Dyspnea | 13 | **Drug Level above Therapeutic** | 8 |
| Tachycardia | 13 | **Drug Screen Positive** | 8 |
| Pulmonary Edema | 11 | Pulmonary Congestion | 8 |

Tachycardia, dyspnea, cardiac arrest, arrhythmia, hypotension and pulmonary edema have been reviewed previously and these events continue to exist in the database in small number of cases. Cardiomegaly, acidosis are unlabeled events, and are reported in small number of cases. It is noted that multiple drug overdose terms were mentioned in cardiac reports.

## B. DIGESTIVE SYSTEM: HEPATIC DISORDERS

*Labeling*[4]
Flexeril labeling contains "abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis" in the Adverse Reaction section.

*AERS*
The AERS database was searched for Flexeril (cyclobenzaprine) hepatobiliary adverse event reports that were received between June 18, 1999 and December 17, 2004, using the MedDRA term, hepatobiliary disorders (SOC) and hepatobiliary investigations (HLGT). AERS contained 32 reports (crude counts) associated with the use of cyclobenzaprine. The 20 most commonly reported adverse event terms are as follows (a report may contain more than one adverse event term):

| | | | |
|---|---|---|---|
| Hepatic Steatosis | 9 | Blood Urea Increased | 5 |
| Coma | 8 | Coagulopathy | 5 |
| Drug toxicity | 8 | **Completed Suicide** | 5 |
| International Normalized Ratio Increased | 8 | Hepatic Enzyme Increased | 5 |
| Alanine Aminotransferase Increased | 7 | Hepatic Failure | 5 |
| **Toxicologic Test abnormal** | 7 | PCo2 decreased | 5 |
| Aspartate Aminotransferase Increased | 9 | Acidosis | 4 |
| Loss of Consciousness | 6 | Blood Creatinine Increased | 4 |
| Multi-organ failure | 6 | Cardiac Arrest | 4 |
| **Multiple drug overdose** | 6 | **Drug Screen Positive** | 4 |

Hepatobiliary dysfunction was reviewed previously and these events continue to exist in the database in small number of cases. It is noted that multiple drug overdose terms were mentioned in hepatobiliary reports.

## C. NERVOUS SYSTEM: SEIZURES

*Labeling*[4]: Seizures are included in the Adverse Reaction section of the product labeling. The other labeled adverse events include ataxia, vertigo, dysarthria, tremors, hypertonia, muscle twitching, convulsion, disorientation, insomnia, depressed mood, abnormal sensation, anxiety, agitation, psychosis, abnormal thinking and dreaming, hallucinations, excitement, paresthesia, diplopia, abnormal gait, delusions, aggressive behavior, alteration in EEG patterns, and extrapyramidal symptoms.

*AERS*

The AERS database was searched for Flexeril (cyclobenzaprine) nervous system adverse events between June 18, 1999 and December 17, 2004, using the MedDRA term, seizures (including subtypes) (HLGT) and nervous system disorders (SOC).

The 20 most commonly reported nervous system adverse event terms under the nervous system disorders (SOC) are as follows (a report may contain more than one adverse event term):

| | | | |
|---|---|---|---|
| Coma | 44 | Depressed level of conciousness | 15 |
| **Overdose** | **22** | Drug Interaction | 15 |
| **Completed suicide** | **21** | **Drug screen positive** | **15** |
| **Drug toxicity** | **18** | Hypotension | 15 |
| Heart rate increased | 18 | Dizziness | 14 |
| Convulsions | 17 | Confusional state | 13 |
| Loss of Consiousness | 17 | Hallucination | 13 |
| **Multiple drug overdose** | **17** | Insomnia | 13 |
| Agitation | 16 | Sedation | 13 |
| Cardiac Arrest | 15 | Vomiting | 12 |

It is noted that drug overdose terms are frequently reported in nervous system adverse event reports.

AERS contained 17 reports (crude counts) of seizures associated with the use of cyclobenzaprine. The most commonly reported adverse event terms are as follows (a report may contain more than one adverse event term):

| | |
|---|---|
| Convulsions | 10 |
| Coma | 7 |
| **Completed suicide** | 6 |
| Grand mal seizure | 6 |
| **Overdose** | 6 |
| **Intentional overdose** | 3 |

Seizures were reviewed previously in the 1999 ODS consult and these events continue to exist in the database in small number of cases. It is noted that intentional drug overdose terms were mentioned in seizure reports.

## VI. CONCLUSIONS

This document provides a recent literature review, crude counts of serious postmarketing adverse event reports associated with the use of cyclobenzaprine, with particular attention to cardiac, hepatobiliary toxicities and seizures, demographic data of all serious reports, and a detailed review of death reports that are unrelated to drug overdoses. Due to the short turnaround time for the request, we did not attempt to match duplicate reports or perform individual case reviews of all adverse event reports.

A total of 438 serious adverse event reports for cyclobenzaprine were retrieved in the AERS database for cyclobenzaprine (Flexeril) between 6/18/1999 and 12/17/2004. The most commonly reported adverse event terms were completed suicide, intentional overdose, and multiple drug overdoses involving coingestion of other medications including narcotics, TCAs, SSRIs, alcohol, narcotics and benzodiazepines. There were 190 females, 175 males, and the gender was unknown in 73 reports. There were 417 US and 9 foreign reports. The outcomes included hospitalization (134), disability (14), life-threatening (15), intervention required (23) and deaths (235).

The majority of the fatal cases (230) involved drug overdoses. Five deaths were unrelated to known drug overdoses. There were two females and three males aged 20, 48, 52, 64, and 81 years who experienced seizure/arrhythmia (1), acute respiratory distress syndrome (1), severe hypoglycemia (1), respiratory arrest (1), or multiple organ failure (1) while receiving cyclobenzaprine. Four cases were confounded by underlying serious medical illnesses (malignancy, diabetes mellitus, alcoholism or biliary cirrhosis), and/or the use of multiple co-suspect medications (multiple chemotherapeutic agents, tramadol) that might have contributed to the events and the fatal outcome. The fifth case provided very limited information. The causal role of cyclobenzaprine in all cases could not be determined.

An overview of AERS crude counts did not provide any new information since the last ODS review (1999). Cardiac, hepatobiliary and seizure adverse event terms were few in number. The adverse event terms related to intentional overdose were frequently listed in cardiac, hepatobilary and seizure reports suggesting a possible role of drug overdose in these cases. Literature searches did not provide additional information.

Cyclobenzaprine use has increased slightly over the last five years with [redacted] prescriptions dispensed in 1999 and [redacted] dispensed in 2003.

In summary, completed suicide and drug overdoses are the most frequently reported serious adverse event terms with cyclobenzaprine in the FDA's AERS database. These findings concur with the findings of the 1999 review.

**REFERENCES**


1. O' Neil BA, Knudson GA, Bhaskara SM. First episode psychosis following cyclobenzaprine use. Can J Psychiatry. 2000 Oct; 45 (8): 763-4
2. Douglass MA, Levine DP. Hallucinations in an elderly patient taking recommended doses of cyclobenzaprine. Arch Intern Med. 2000 May 8; 160 (9): 1373
3. Winek CL Jr, Wahba WW, Winek CL. Drowning due to cyclobenzaprine and ethanol. Forensic Sci Int. 1999 March 15; 100 (1-2): 105-8
4. Cyclobenzaprine (Flexeril) Product Labeling. Alza Corporation. March 2004.

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/s/
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Renan Bonnel
1/14/05 02:27:54 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
1/18/05 10:08:04 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-777

ECR Pharmaceuticals
Attention: Robert G. Ferraino
Regulatory Affairs
404 Saw Mill Rd.
East Berne, NY 12059

Dear Mr. Ferraino:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for AMRIX® (cyclobenzaprine hydrochloride extended-release capsules) 15 mg and 30 mg.

We also refer to the meeting between representatives of your firm and the FDA on May 4, 2005. The purpose of the meeting was to review and discuss the responses to the Approvable Letter of February 28, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Paul Z. Balcer, Regulatory Project Manager, at (301) 827 2090.

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Appears This Way
On Original

# Meeting Minutes

**MEETING DATE:** May 4, 2005

**TIME:** 12:00-1:00 p.m.

**LOCATION:** S300, 9201 Corporate Boulevard, Rockville, MD 20850

**APPLICATION (DRUG):** NDA 21-777 AMRIX (cyclobenzaprine HCl), 15 & 30 mg Capsule

**SPONSOR:** ECR Pharmaceuticals/ [redacted]

**TYPE OF MEETING:** Type B, face-to-face

**MEETING CHAIR:** Sharon Hertz, M.D.

**MEETING RECORDER:** Paul Z. Balcer

**MEETING OBJECTIVE:** [redacted], acting as the Agent for ECR Pharmaceuticals, Inc., requests FDA review and discuss the responses to the Approvable Letter of February 28, 2005.

**BACKGROUND:**
**Meeting request:** March 8, 2005, received March 11, 2005
**Meeting package:** April 11, 2005, received March 12, 2005

The NDA was submitted on April 29, 2004, received April 30, 2004. The PDUFA review goal date was February 28, 2005 (10 month standard review). An Approvable Letter was sent to sponsor on February 28, 2005. The sponsor requested a face-to-face meeting on March 8, 2005.

**FDA Attendees**

| Name | Title |
|---|---|
| Brian E. Harvey, MD, PhD | Outgoing Acting Division Director, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550 |
| Bob Rappaport, MD | Incoming Division Director, Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170 |
| Sharon Hertz, MD | Deputy Director, HFD-550 |
| James P. Witter, MD, PhD | Assigned Clinical Team Leader |
| Christina Fang, MD | Assigned Clinical Reviewer |
| Sue-Ching Lin, RPh | Chemistry Reviewer |
| Abi Adebowale, PhD | Clinical Pharmacology & Biopharmaceutics Reviewer |
| Paul Z. Balcer | Regulatory Project Manager |

**External Constituent Attendees**

| Name | Title |
|---|---|
| Davis Caskey | ECR Pharmaceuticlas, VP Pharmaceutical Operations |
| Janis Hardin | Mgr., Pharm. Administration |
| Robert Murphy, PhD | VP, Product Development |
| | |
| | |
| Robert Ferraino | ECR Consultant, Regulatory |
| | |
| Bhanu Balasubramaniam, PhD | Eurand, Regulatory Affairs |
| Mike Markham, PhD | Eurand, Assoc. Director, Analytical |
| Karen Siefert | Eurand, Regulatory Affairs Specialist |
| | |

## AGENDA QUESTIONS FROM SPONSOR:

**Deficiency #1 Question**

Patient assessments from the combined clinical studies reflect statistically significant levels of efficacy and a dose response for both Amrix 15 and Amrix 30, and all clinical studies, both individually and in the aggregate, demonstrated favourable efficacy comparisons between the Amrix extended release formulations and the long marketed Flexeril product. Would the sponsor's commitment to conduct a pre-approved, acceptably designed post-marketing study which further documents the efficacy of the Amrix extended release formulations, be sufficient to grant registration of the Amrix dosage forms?

FDA Comment:
We note that the subject's rating of medication helpfulness, one of the primary efficacy parameters, demonstrated statistically significant differences between each dose level and the placebo arm on day 4 (as well as on day 8 and 14) based on pooled data. On re-evaluation of physician's global assessment and each component of the physician's global based on pooled data, the parameter appeared to be insensitive in detecting any treatment difference. While evaluation of efficacy using pooled data is not commonly accepted, as this is a 505(b)(2) application, we will consider reviewing the evidence for efficacy based on pooled data from the 2 studies of identical design, provided that all the PK issues and safety issues are adequately addressed.

***Additional meeting comments*:**
**The sponsor noted the division's response. The division clarified for the sponsor that the complete response to the approvable action must address all of the deficiencies at the resubmission of the NDA.**

**Deficiency #2 Questions**

1. The Sponsor believes that equivalence in bioavailability has been demonstrated in this study. Does the Agency agree with this conclusion?

   FDA Comment:
   No, we do not agree. The bioequivalence that was demonstrated in study 1107 was based on the comparison between your product and an altered formulation of the Flexeril® IR tablet. The relevance of this finding of equivalence is unknown because there is no direct comparison of the altered formulation with the intact approved Flexeril® tablet in the same study to bridge the information.

   The cross-study comparison of the bioavailability of the intact Flexeril® tablet in pilot study 1101 with the altered formulation received by the younger age group selected from study 1107, indicated that the altered formulation had a higher systemic exposure ($C_{max}$ and AUC). Therefore a comparable systemic exposure bridge between the intact approved product and the altered encapsulated tablet was not established.

   Based on the aforementioned, you need to conduct a single-dose relative bioavailability study of the to-be-marketed formulation of the Amrix® capsules versus the approved intact Flexeril ® tablet at an equivalent dose, administered according to the current approved package insert.

   ***Additional meeting comments*:**
   **The division noted that the cross study comparisons suggest that the adulterated, crushed Flexeril and the unadulterated intact approved Flexeril tablets are not bioequivalent. As a result, direct comparison between unadulterated Flexeril and Amrix capsules is necessary. This could be achieved by designing an open-label PK study which would examine the approved Flexeril IR intact product (TID or q8 hours for a day) versus Amrix (single dose). The study should enrol a representative study population, composed of the young and the elderly (≥65 yrs old). The division suggested the sponsor include an arm of the adulterated Flexeril tablets in the study. If the unadulterated and adulterated Flexeril are bioequivalent, then the need for further PK study (especially the steady state study) would be further evaluated.**

2. Does the Agency agree with the Sponsor that the data presented above suggests similar linear pharmacokinetics and comparable bioavailability between the ER cyclobenzaprine formulation following single doses and at steady-state?

   FDA Comment:
   We do not agree. Please clarify what you mean by linearity.

   In addition, the results of the one-week, bioavailability/bioequivalence study 1104 were compromised by the use of altered IR formulation, the omission of the last two doses of the IR 10 mg product in the last 24-hour period, and the selection of a non-representative study population (no elderly enrolled in the study).

*Additional meeting comments*:

**The sponsor explained that linearity refers to the linear kinetics that were observed for the AUC for the Amrix capsules. The AUC of the single dose was comparable to that obtained at the steady state.**

**The division noted that because of the drug accumulation represented by the increased $C_{max}$ with repeated dosing, single-dose and steady state bioavailability of ER formulation were not comparable. Additionally, the sponsor needs to consider the potential safety problems associated with the prolonged half-life in the elderly population compared to younger adults. The failure to reach steady state in the elderly patients because of the nearly 50 hour half-life was noted by the division as a deficiency that would also require additional evaluation.**

3. Does the Agency agree with the Sponsor that the extrapolations of the findings from Study 1107 to Study 1104 are valid and that the ER formulation demonstrates comparable bioavailability to the IR formulation at steady-state?

   FDA Comment:
   No, because of the deficiencies identified in study 1107 and 1104 the extrapolations are not considered valid.

4. Does the Agency agree with the Sponsor that from a pharmacokinetic viewpoint that the $C_{maxss}$ does not represent a safety issue?

   FDA Comment:
   No, we do not agree. Drug accumulation upon repeated dosing as indicated by an increase in Cmax of at least two fold after one-week exposure as compared to the single-dose Cmax is a safety concern. The increase in Cmax is considered a more serious concern in the elderly because it was demonstrated that this population had a prolonged mean $t_{1/2}$ of 49 hours following a single dose administration. The elderly also had a higher exposure in terms of AUC. Therefore at steady state it is expected that the elderly may take longer to achieve steady state and, they may also have a higher exposure due to drug accumulation which would represent a potential increase in the risk of drug-related toxicities.

   Based on the aforementioned (Parts 2, 3 and 4), you need to conduct a multiple-dose safety trial in a representative population that would incorporate pharmacokinetic sampling. The study should be of sufficient duration to ensure that steady-state levels had been achieved and should include both the to-be-marketed formulation of the Amrix® capsules and the approved intact Flexeril ® tablet.

*Additional meeting comments*:

**Deficiency #3 Questions**

Does the above information and proposed amended labeling appropriately respond to the noted deficiency?

FDA Comment:

**Deficiency #4 Question**

Does the Agency concur with this approach?

FDA Comment:
Yes, we agree with this approach. Basically, the time point specification range at the 4 and 8 hr originally proposed deviated by > ±10 % from the mean dissolution profile obtained for the clinical batches. The specifications we proposed were to tighten the range to be within ±10 % based on the dissolution data for the pivotal clinical batches provided, and according to the recommendations in the Guidance for Industry quoted by the sponsor. Please note that the recommended range for the 4hr time point has a typographical error in it. It should read as follows: *4-hr=* ——— and not /——

***Additional meeting comments*:**
**The sponsor was asked to submit data on the batches used in the clinical and bioavailability studies and that they intend to use to set their dissolution specifications.**

**Deficiency #5 Question**

*Additional meeting comments*

**The division agreed to look at proposed PK studies and provide feedback to the sponsor.**

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/s/

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Sharon Hertz
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signing for Bob Rappaport, M.D.

# TELECONFERENCE MEMORANDUM

**DATE, TIME:** February 1, 2005, 11:30 a.m. – 12:15 p.m.

**APPLICATION:** NDA 21-777
**DRUG:** AMRIX (cyclobenzaprine HCl)
**INDICATION:** Relief of muscle spasms

**BETWEEN:** ECR Pharmaceuticals

- Mr. Davis Caskey, - VP, Pharmaceutical Operations, ECR Pharmaceutical
- Bhanu Balasubramaniam - Regulatory Affairs Manager, Eurand
- Mike Markam – Analytical, Eurand
- Bill Webb – Quality, Eurand
- Karen Siefert – Regulatory Affairs, Eurand
- [redacted]
- [redacted]
- [redacted]

**AND**

Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP)

- John Smith, Ph.D. - Chemistry Team Leader
- Sue-Ching Lin, M.S., R.Ph., Chemistry Reviewer
- Paul Balcer, Project Manager

**OBJECTIVE:** **Discussion and clarification of CMC Information Request letters of November 17 and January 28, 2005, and sponsor's December 17, 2004 response.**

**BACKGROUND:**

- On November 17, 2004 FDA sent a CMC Information Request letter.
- On December 17, 2004 the sponsor responded to the November 17, 2004 CMC IR letter.
- On January 28, 2005 FDA sent a follow up CMC Information letter with a request for a teleconference.

**DISCUSSION:**

Ms. Lin informed the sponsor that the drug substance should be tested for impurities in accordance with ICH Q3A guideline and FDA "Guidance for Industry, NDAs: Impurities in Drug Substances" because the drug product is a new drug dosage form (extended-release). The analytical procedure for the HPLC method for impurities should be provided in the NDA.

The applicant asked whether the TLC impurity test as per USP monograph for cyclobenzaprine hydrochloride will need to be performed and included in the specification. The FDA responded that since it is included in the USP monograph, it needs to be performed. The applicant was advised to submit the HPLC method for impurities to the USP to substitute the current TLC method.

The sponsor was asked to provide a table clearly stating specifications for the drug product and drug substance, including 1) a list of tests, 2) references to analytical procedures, and 3) acceptance criteria.

The sponsor was informed that the proposed reduced testing frequency for annual production batches was not acceptable and that according to the ICH Q1A guidance, batches on stability should be tested every three months during the first year, every 6 months during the second year, and annually thereafter.

The sponsor was advised to state in a revised protocol that stability studies will be performed on each strength in the smallest and the largest sizes for each container closure system.

The sponsor was advised that a stability commitment needs to be provided documenting continued stability studies on the registration batches through the sponsor's proposed expiration date. The stability results need to be reported to the FDA in NDA annual reports.

**ACTION ITEM:**

- The Sponsor will provide clarification and written responses to the above inquiries.

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/s/

Carmen DeBellas
2/28/05 02:41:56 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 10/21/05

TO: Paul Z. Balcer, Regulatory Project Manager
Christine Fang, M.D., Clinical Reviewer
Division of Anesthesia, Analgesia, and Rheumatology Drug Products, HFD-170

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Dianne D. Tesch
Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-777

APPLICANT: ECR Pharmaceuticals

DRUG: Amrix ® (cyclobenzaprine 15 and 30 mg modified release CMR)

CHEMICAL CLASSIFICATION: 3S

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Muscle Relaxant



CONSULTATION REQUEST DATE: August 30, 2005

ACTION GOAL DATE: 10/30/05

PDUFA DATE: 2/28/06

I. BACKGROUND:

In this NDA, the report for Study 1107 indicated that ground and encapsulated Flexeril was used

as the comparator product in the above referenced study. The sponsor now contends that the investigator used intact Flexeril and not product that was ground and encapsulated. The Division of Anesthesia, Analgesia, and Rheumatology Products requests a site visit to determine the manner in which Flexeril was used during this study.

This was a Phase I safety and PK study. Dr. Gutierrez was the only researcher for Study 1107. She enrolled approximately 36 subjects. She is a high volume researcher, with 120 studies listed in the Clinical Investigator System (CIS) data base. Dr. Gutierrez has three prior inspections performed by the Good Laboratory Practices/Bioequivalence Branch, in 2000, 2002, and 2004. One inspection was classified NAI, and the other two were VAI. According to the FDA inspector, deficiencies noted at prior inspections have been resolved.

II. RESULTS (by protocol/site):

| NAME | CITY | STATE | ASSIGNED DATE | RECEIVED DATE | CLASSIFICATION |
|---|---|---|---|---|---|
| Maria J. Gutierrez | Ft. Lauderdale | FL | 8/30/05 | 10/19/05 | NAI |
| Eurand, Inc. | Vandalia | OH | 8/30/05 | 1024/05 | NAI |

A. Protocol CMR 1107: "A Randomized Open-Label, Two-Period Crossover Study to Compare the Safety and Pharmacokinetics of Cyclobenzaprine HCl Modified Release (CMR) 30 mg Once Daily and Cyclobenzaprine HCl 10 mg Three Times Daily in Healthy Volunteers"

1. Site #1 Maria Gutierrez, M.D., Fort Lauderdale, FL. The data are acceptable.

   a. The inspection revealed that Flexeril was administered in intact tablet form and not ground and encapsulated as initially reported in the NDA study report. The investigational drug Amrix® was administered in capsule form. 65 subjects were screened, thirty six enrolled, and 2 withdrew consent. 12 of 36 records were reviewed in depth for data integrity and adherence to protocol.

   b. No limitations were encountered.

   c. There was no evidence of under reporting of adverse events or other violations that might have affected data integrity.

2. Site #2 Eurand, Inc., Vandalia, OH. The data and information were acceptable.

   a. The firm manufactured three lots of cyclobenzaprine HCl Modified Release capsules and placebo capsules for the study. The firm sent the batches to [redacted] for [redacted]

   b. No limitations were encountered.

   c. There was no evidence of manufacturing irregularities.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

There were no significant problems found at either Dr. Gutierrez's site or at the manufacturing site. According to Dr. Gutierrez and her staff intact Flexeril tablets were used at her site. The manufacturer, Eurand, says that ground and encapsulated Flexeril was shipped to the ——— ——— . A separate investigation of the ——— site was not ordered.

Dianne D. Tesch
GCPB Reviewer Name
Title

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/
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Dianne Tesch
10/26/2005 08:11:20 AM
CSO

Leslie Ball
10/27/2005 12:12:00 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-777

**INFORMATION REQUEST LETTER**

Dear [redacted]

Please refer to your April 29, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AMRIX® (cyclobenzaprine hydrochloride extended-release capsules) 15 mg and 30 mg.

We have reviewed your December 17, 2004 submission, in response to the Chemistry, Manufacturing and Controls information request letter of November 17, 2004, and have additional comments and information requests (the numbers correspond to those in information request #1, which are also your response numbers).

1(a): Please add a hyphen (which was inadvertently left out in the last information request letter) between "extended" and "release" to be consistent with the USP monograph nomenclature convention.

1(b): The statement that Eurand only performed a "one-time" test for impurities in the drug substance and will not test drug substance batches in the future appears to be inconsistent with cGMP (see 21 CFR 211.84(a) and 21CFR 211.84(d)(2)). A drug product manufacturer may accept test results from a supplier of a component only if the reliability of the supplier's analyses is periodically verified. Since testing for impurities should be included in the drug substance specification (see next comments), Eurand should be prepared to either test every batch of drug substance for impurities, or to incorporate the testing of impurities into a drug substance supplier validation program. In either case, a mechanism must be established to make sure that every batch of drug substance conforms to the specification approved in the NDA.

Provide a detailed analytical procedure for testing impurities in the drug substance, along with the validation of the method and the reference standards used in the analytical procedure. It is not sufficient to simply reference to the analytical procedure for the drug product. The reference standard used for the assay of the drug substance should also be provided.

1(c) and 1(d): Provide a drug substance specification sheet, not a blank COA. See 3(a) below for the comments about the format of the specification. Each USP test should be individually listed with its USP general chapter number (e.g., USP<731> for *Loss on Drying*). Eurand's method number for testing related substances should be listed. It is not acceptable to "transcribe from manufacturer's COA."

3(a): Provide a drug product specification that clearly and unambiguously lists the tests, analytical procedures, and acceptance criteria that will be used to determine whether a batch of drug product is acceptable for its intended use. We recommend that you adopt a format similar to what appears in the first three columns of the table on page 77, volume 8, except that the column headings should be labeled "tests," "analytical procedures," and "acceptance criteria." Any specified unidentified impurity included in the specification should be specified by, for example, relative retention time. We also strongly recommend that each analytical procedure have its unique identification number.

3(b): (i) Revise the stability protocol to indicate that (a) batches on stability will be tested every three months over the first year, every 6 months over the second year, and annually thereafter, and (b) stability studies will be performed on each strength in the smallest and the largest sizes for each container closure system (i.e., bottle and blister). (ii) Provide a stability commitment to continue stability studies on the three registration batches through the expiration dating period, submit results to the FDA in NDA annual reports, and withdraw from the market any lots found to be fall outside the specification (refer to ICH Q1A and FDA stability guidances).

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Paul Z. Balcer, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

John Smith, Ph.D.
Chemistry Team Leader
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
DNDC DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

---

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/s/

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John Smith
1/28/05 03:47:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-777

**INFORMATION REQUEST LETTER**

Dear [redacted]

Please refer to your April 29, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AMRIX® (cyclobenzaprine HCl) 15 and 30 mg Extended Release.

We are reviewing the Statistical section of your submission and have the following comments and information requests.

*Please provide us with full descriptions for variables and variable values in all the raw or derived SAS data sets used for the primary efficacy (e.g., subject's rating of medication helpfulness & physician's clinical global assessments) and secondary efficacy analyses (e.g., subject rated relief from local pain, etc).*

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Paul Z. Balcer, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and Ophthalmic
Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

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Carmen DeBellas
1/6/05 10:02:57 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# REQUEST FOR CONSULTATION

TO *(Division/Office)*:
**Mail: ODS (Room 15B-08, PKLN Bldg.)**

FROM: Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550), Christina Fang, M.D., Medical Reviewer

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT: |
|---|---|---|---|---|
| December 20, 2004 | N/A | 21-777 | Original documentation | April 30, 2004 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| AMRIX (cyclobenzaprine HCl) | Standard | 5030300 | January 31, 2005 |

NAME OF FIRM:ECR Pharmaceuticals

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:
  Post Marketing Risk Management Program

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

| ☐ CLINICAL | ☐ PRECLINICAL |
|---|---|

**COMMENTS/SPECIAL INSTRUCTIONS:**

Please also provide recommendations on the program for _____ for NDA 21-777

\\CDSESUB1\N21777\N_000\2004-12-10 located under Item 3)

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) |
|---|---|
| Christina Fang, M.D., Medical Officer/Brian E. Harvey, M.D., Ph.D., Acting Division Director on behalf of Sharon Hertz, M.D., Deputy Director | ☐ MAIL ☒ E-MAIL ☐ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER:<br>Paul Z. Balcer, Project Manager |

---

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/s/
---
Christina Fang
12/27/04 11:41:08 AM

Brian Harvey
12/30/04 08:50:07 PM

3 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

✓ Deliberative Process

*Withheld Track Number: Administrative-* 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-777

**INFORMATION REQUEST LETTER**

ECR Pharmaceuticals, Inc.

Dear [redacted]

Please refer to your April 29, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AMRIX (cyclobenzaprine HCl) 15 and 30 mg Modified Release.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA to the following:

1. Provide the results of statistical analysis of the treatment comparison between the active control, cyclobenzaprine HCl 10mg TID, and placebo for all the primary and secondary efficacy parameters

2. Provide the results of statistical analysis of the treatment comparison between each of the active treatments and placebo (i.e., between cyclobenzaprine MR 30mg and placebo, cyclobenzaprine MR 15mg and placebo, and cyclobenzaprine 10mg TID, and placebo, respectively), in terms of physician's assessment of muscle spasm, presence of local pain, limitation of range of motion, and limitation of activities of daily living. According to the protocol each of the parameters listed should have been recorded separately in addition to being used in formulating physician's global assessment.

3. In terms of reasons for discontinuation from the study, provide the number and percentage of discontinuation due to lack of efficacy. Explain the term *discontinuation due to sufficient response versus discontinuation due of insufficient response*, specify the administrative reasons and provide meaningful and detailed terms for the "other" reasons for discontinuation (13 days of dosing is the length of exposure, which is not considered a reason for discontinuation).

If you have any questions, call Paul Z. Balcer, Regulatory Health Project Manager, at 301-827-2504.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/
Carmen DeBellas
12/17/04 12:40:26 PM

A21777 RequestforacopyoftheMarch312003emailcommunicationfromsponsortoFDArelatingtoIND62261.txt
MessageFrom: Balcer, Paul
Sent: Thursday, December 09, 2004 11:18 AM
To: '
Subject: RE: NDA 21-777 AMRIX (cyclobenzaprine HCl) - Request for a copy of the March 31, 2003 e-mail communication from sponsor to FDA relating to IND 62,261.

Importance: High
Sensitivity: Confidential

Dear

Thank you for your holiday wishes and likewise, please accept mine. Additionally, thank you for letting me know that I should be expecting sponsor's responses next Monday.

I received a request for a copy of a March 31, 2003 e-mail communication between our Division and ECR Pharmaceuticals, Inc. This e-mail exchange was with one of our project managers, Nancy Halonen (she is no longer with the FDA). The background for the e-mail request stems from an entry in the NDA, in Volume 20, on page 98, second paragraph:
"Communication with the Agency was established with respect to Protocol 1104, On Monday, March 31, 2003, when it was realized that the total area under the plasma cyclobenzaprine concentration vs. time curve for the IR formulation was not available over the 24-hour dosing cycle. The Agency indicated it would be appropriate to focus instead on the elimination rate and the total body clearance since estimates of AUC 0-tss over a 24-hour dosing cycle were not available for the IR information."

If you have any questions, please contact me.

Regards,

Paul

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Paul Z. Balcer
Regulatory Health Project Manager
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
FDA/CDER/ODEV
Phone: (301) 827 2090
Fax: (301) 827 2531
E-mail: balcerp@cder.fda.gov

-----Original Message-----
From: [mailto:
Sent: Thursday, December 09, 2004 10:42 AM
To: 'Balcer, Paul'
Cc: 'DeBellas, Carmen'
Subject: RE: NDA 21-777 AMRIX (cyclobenzaprine HCl) - Clarification of the December 2, 2004 Information request - CLINICAL.
Sensitivity: Confidential

Dear Paul

Thank you for your responses. May I ask that you please call me and not I never use the title with anyone if it isn't absolutely necessary.

On our end, we are trying to get the package to the Agency by Monday, December 13. If there is any delay I will let you know. I don't, however, expect any delays.

Let me take this opportunity to wish you and your family a happy holiday season just in case we don't communicate again until after the holiday season.

Best regards,

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-----Original Message-----
From: Balcer, Paul [mailto:BalcerP@cder.fda.gov]
Sent: Thursday. December 09, 2004 9:37 AM
To: '
Cc: DeBellas, Carmen
Subject: RE: NDA 21-777 AMRIX (cyclobenzaprine HCl) - Clarification of the December 2, 2004 Information request - CLINICAL.
Importance: High
Sensitivity: Confidential

Dear

Thank you for your prompt response. Below are answers to your questions:

1. Sponsor's responses to information requests are amendments but they are considered minor amendments and do not extend the clock.

2. The NDA was classified as a paper submission. The electronic submissions are for reviewers' cutting/pasting of tables to make the review easier, however all electronic files need to be sent to the e-doc room for NDAs.

3. Please attempt to send information before the Christmas Holidays. The clinical information requests of December 3, 2004 are critical because other divisions are involved in the review and inspection.

If you have further questions, please contact me.

Regards,

Paul Z. Balcer

Regulatory Health Project Manager

Division of Anti-Inflammatory, Analgesic

and Ophthalmic Drug Products (HFD-550)

FDA/CDER/ODEV

Phone: (301) 827 2090

Fax: (301) 827 2531

E-mail: balcerp@cder.fda.gov



-----Original Message-----
From: [redacted] [mailto:[redacted]
Sent: Monday, December 06, 2004 8:20 AM
To: Paul Balcer
Subject: FW: NDA 21-777 AMRIX (cyclobenzaprine HCl) - Information request - CLINICAL.
Importance: High
Sensitivity: Confidential

Dear Paul

This is to confirm that I received your e-mail. I am trying to arrange a meeting of all parties today to discuss the Clinical. The information for the CMC is currently being worked on.

1. Am I correct in that both the request for information letter received with respect to CMC (dated November 17, 2004) and the e-mail received for Clinical (December 3, 2004) are not Amendments but are responses to requests for information. Could you please confirm this.

2. The April 29, 2004 NDA 21-777 application was a paper submission. The "desk copy" CD ROM was a courtesy copy provided to you to help any of the reviewers facilitate their review. We can certainly submit them electronically in our Clinical Package Response if you desire this. However, I don't want to confuse the issue that NDA 21-777 was a paper submission. Could you please confirm you want the protocols and reports submitted electronically to the Document Room.

3. The other item I need to mention is Item 2 of your e-mail. It would appear that it would by physically impossible to do the necessary searches on Flexeril IR, physically obtain the reports, and comply it in a meaningful way by December 10th. I do understand why this issue is in your letter as I recognize the significance being accorded to the dose exposure-response-safety relationship.

---

I will try and call you after I meet with the ECR and ——— people today. In the interim, could you please let me know about item 1 and 2 above.

Best regards,

———

———

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-----Original Message-----
From: Balcer, Paul [mailto:BalcerP@cder.fda.gov]
Sent: Friday, December 03, 2004 4:53 PM
To: '———'
Subject: NDA 21-777 AMRIX (cyclobenzaprine HCl) - Information request - CLINICAL.
Importance: High
Sensitivity: Confidential

———

Please refer to your April 29, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AMRIX® (cyclobenzaprine HCl), 15 and 30 mg modified release capsules.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide a list of investigators and the address of each study site along with the number of patients enrolled at each site for the study 1105.

2. Provide safety summaries of Flexeril IR in terms of the AE rates, severity, serious outcomes, and relationship with the level and the length of exposure, whenever applicable, from the following sources:

- post marketing clinical trials
- post marketing epidemiological studies
- post marketing spontaneous reports
- literature reports

3. [redacted]

Additionally, while reviewing the submissions to electronic document room, we were unable to locate the electronic versions of the study protocols and reports, which were part of the "desk copy" CD ROM containing labeling.

The Division reminds you that there are less than 3 months left in the review clock.

Please provide this information as official submission and electronically, if possible, as soon as possible but no later than December 10, 2004. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
9201 Corporate Blvd.
Rockville, MD 20850-3202
Phone: (301) 827 2504
Fax: (301) 827 2531
paul.balcer@fda.hhs.gov

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/s/
---
Paul Balcer
1/18/05 11:55:33 AM
CSO

77CorrespondenceE-mail TO SponsorNDA21777ClarificationoftheDecember22004CInformationrequest120
MessageFrom: Balcer, Paul
Sent: Thursday, December 09, 2004 9:37 AM
To: [redacted]
Cc: DeBellas, Carmen
Subject: RE: NDA 21-777 AMRIX (cyclobenzaprine HCl) - Clarification of the December 2, 2004 Information request - CLINICAL.

Importance: High
Sensitivity: Confidential

Dear [redacted]

Thank you for your prompt response. Below are answers to your questions:

1. Sponsor's responses to information requests are amendments but they are considered minor amendments and do not extend the clock.

2. The NDA was classified as a paper submission. The electronic submissions are for reviewers' cutting/pasting of tables to make the review easier, however all electronic files need to be sent to the e-doc room for NDAs.

3. Please attempt to send information before the Christmas Holidays. The clinical information requests of December 3, 2004 are critical because other divisions are involved in the review and inspection.

If you have further questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products (HFD-550)
FDA/CDER/ODEV
Phone: (301) 827 2090
Fax: (301) 827 2531
E-mail: balcerp@cder.fda.gov



-----Original Message-----
From: [redacted] [mailto:[redacted]]
Sent: Monday, December 06, 2004 8:20 AM
To: Paul Balcer
Subject: FW: NDA 21-777 AMRIX [redacted] - Information request - CLINICAL.
Importance: High
Sensitivity: Confidential

Dear Paul

This is to confirm that I received your e-mail. I am trying to arrange a meeting of all parties today to discuss the Clinical. The information for the CMC is currently being worked on.

1. Am I correct in that both the request for information letter received with respect to CMC (dated November 17, 2004) and the e-mail received for Clinical (December 3, 2004) are not Amendments but are responses to requests for information. Could you please confirm this.

2. The April 29, 2004 NDA 21-777 application was a paper submission. The "desk copy" CD ROM was a courtesy copy provided to you to help any of the reviewers facilitate their review. We can certainly submit them electronically in our Clinical Package Response if you desire this. However, I don't want to confuse the issue that NDA 21-777 was a paper submission. Could you please confirm you want the protocols and reports submitted electronically to the Document Room.

3. The other item I need to mention is Item 2 of your e-mail. It would appear that it would by physically impossible to do the necessary searches on Flexeril IR, physically obtain the reports, and comply it in a meaningful way by December 10th. I do understand why this issue is in your letter as I recognize the significance being accorded to the dose exposure-response-safety relationship.

I will try and call you after I meet with the ECR [redacted] people today. In the interim, could you please let me know about item 1 and 2 above.

Best regards,

[redacted]

[redacted]

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-----Original Message-----
From: Balcer, Paul [mailto:BalcerP@cder.fda.gov]
Sent: Friday, December 03, 2004 4:53 PM
To: [redacted]
Subject: NDA 21-777 AMRIX (cyclobenzaprine HCl) - Information request - CL INICAL.
Importance: High
Sensitivity: Confidential

77CorrespondenceE-mail TO SponsorNDA21777ClarificationoftheDecember22004CInformationrequest120

Please refer to your April 29, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AMRIX® (cyclobenzaprine HCl), 15 and 30 mg modified release capsules.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1.. Provide a list of investigators and the address of each study site along with the number of patients enrolled at each site for the study 1105.
2.. Provide safety summaries of Flexeril IR in terms of the AE rates, severity, serious outcomes, and relationship with the level and the length of exposure, whenever applicable, from the following sources:
a.. post marketing clinical trials
b.. post marketing epidemiological studies
c.. post marketing spontaneous reports
d.. literature reports
3.

Additionally, while reviewing the submissions to electronic document room, we were unable to locate the electronic versions of the study protocols and reports, which were part of the "desk copy" CD ROM containing labeling.

The Division reminds you that there are less than 3 months left in the review clock.

Please provide this information as official submission and electronically, if possible, as soon as possible but no later than December 10, 2004. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
9201 Corporate Blvd.
Rockville, MD 20850-3202
Phone: (301) 827 2504
Fax: (301) 827 2531
paul.balcer@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-777

**INFORMATION REQUEST LETTER**

Dear [redacted]

Please refer to your April 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AMRIX® (cyclobenzaprine HCl) 15 and 30 mg Modified Release Capsules.

We are reviewing the clinical pharmacology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

*The sponsor has used an altered approved product (i.e. Flexeril 10 mg tablets) as its Reface Listed Drug in the PK studies and, its' active control in the clinical studies. However, it is not clear from the data submitted how the sponsor determined that this alteration to the approved drug product would not affect its systemic exposure. Please provide information that demonstrates that altering the Flexeril tablets does not affect its systemic exposure. This may be provided as in vivo or in vitro data or both.*

If you have any questions, call Paul Z. Balcer, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

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Carmen DeBellas
12/8/04 01:55:08 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# REQUEST FOR CONSULTATION

TO *(Division/Office)*:
**Mail: ODS (Room 15B-08, PKLN Bldg.)**

FROM: Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550), Christina Fang, M.D., Medical Reviewer

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT: |
|---|---|---|---|---|
| December 7, 2004 | N/A | 21-777 | Original documentation | April 30, 2004 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| AMRIX (cyclobenzaprine) | Standard | 5030300 | January 20, 2005 |

NAME OF FIRM:ECR Pharmaceuticals

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

Post marketing safety assessment for Flexeril IR from introduction to market until present.

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

Amrix is an extended-release formulation of cyclobenzaprine HCl (Flexeril is a brand name). The Sponsor has submitted NDA 21-777 as a 505(b)(2) application and did some PK and clinical studies on the ER formulation. Because they are using the Flexeril safety data base for support of the new formulation, would you please review the post marketing safety data (spontaneous reports, literature, and epidemiological studies) to identify safety signals or emerging safety concerns with the use of Flexeril IR.

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) |
|---|---|
| Christna Fang, M.D., Medical Officer/Sharon Hertz, M.D., Deputy Director (HFD-550) | ☐ MAIL ☒ E-MAIL ☐ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER: |

| | |
|---|---|
| | Paul Z. Balcer, Project Manager |

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/s/

Sharon Hertz
12/8/04 12:30:23 PM

NDA 21-777CorrespondenceE-mail TO SponsorNDA21777CMCclarificationof11172004IRletter120304.txt
MessageFrom: Balcer, Paul
Sent: Friday, December 03, 2004 3:04 PM
To: [redacted]
Subject: RE: NDA 21-777 AMRIX (cyclobenzaprine HCl) - CMC clarification of the November 17, 2004 Information Request letter.

Importance: High
Sensitivity: Confidential

Dear [redacted]

The following is the clarification to Dr. Smith's Information Request letter of November 17, 2004:

The drug should never be placed on the market as "modified release capsules." The sponsor needs to provide written documentation to show that this will not occur. At a minimum, when FPL is submitted, the name of the drug on the FPL should be "extended release capsules," not "modified release."

Draft labels and labeling, should be revised as soon as possible to say "extended release" and submitted for review.

When responding to other chemistry deficiencies, the sponsor needs to include a statement to the effect that they will revise the labels and labeling as requested, and submit them in a future amendment.

If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
9201 Corporate Blvd.
Rockville, MD 20850-3202
Phone: (301) 827 2090
Fax: (301) 827 2531
paul.balcer@fda.hhs.gov

-----Original Message-----
From: [redacted] [mailto:[redacted]
Sent: Monday, November 22, 2004 10:30 AM
To: Paul Balcer
Subject: NDA 21-777
Importance: High



[redacted]

NDA-21-777

Dear Paul

Just an e-mail to confirm that we have received the letter from the Agency (Dr. John Smith) with request to CMC items for NDA 21-777. We are assembling the responsible people and as soon as we can assess the availability of people and amount of work required to respond I will be able to inform you of a probable date that the Agency will receive the response.

One item on Dr. Smith's letter refers renaming the product to "XXX extended release capsules" in place of "modified release capsules". We are not sure as to whether Dr. Smith is requesting that we confirm this will eventually be done in all labels and labeling or if he wants us to resubmit the labels and labeling with the new nomenclature (along with the additional material requested in his letter). It appears from the letter that he is suggesting the former but we would like to confirm that is his intention.

Could you possible address this item with him and let me know how he responds. Have a nice holiday season.

Best regards,

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

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/s/

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Paul Balcer
2/25/05 01:04:25 PM
CSO

# NDA REGULATORY FILING REVIEW
**(Including Memo of Filing Meeting)**

NDA # 21-777 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: AMRIX®
Generic Name: Cyclobenzaprine HCl modified release
Strengths: 15 and 30 mg Tablet

Applicant: ECR Pharmaceuticals, c/r

Date of Application: April 29, 2004
Date of Receipt: April 30, 2004
Date clock started after UN:
Date of Filing Meeting: June 22, 2004
Filing Date: June 29, 2004
Action Goal Date (optional): User Fee Goal Date: February 28, 2004

Indication(s) requested: Adjunct therapy to rest and physical therapy for relief of muscle spasms, associated with acute, painful musculoskeletal conditions.

Type of Original NDA: (b)(1) _____ (b)(2) ___X_____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

***NOTE:***

*(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*

*(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

____ NDA is a (b)(1) application OR ___ NDA is a (b)(2) application

Therapeutic Classification: S _X_____ P _____
Resubmission after withdrawal? ____N/A__ Resubmission after refuse to file? ___N/A_____
Chemical Classification: (1,2,3 etc.) _____3___
Other (orphan, OTC, etc.) ___N/A_____

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

User Fee Status: Paid _____ Exempt (orphan, government) __505(b)2
Waived (e.g., small business, public health) __X(small business)

***NOTE:*** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication*

*for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application?

  YES X NO

  If yes, explain:

  Three years exclusivity

- Does another drug have orphan drug exclusivity for the same indication? YES NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

  YES NO

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO X
  If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES X NO

- Was form 356h included with an authorized signature? YES X NO
  **If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES X NO

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A X YES NO
  **If an electronic NDA, all certifications must be in paper and require a signature.**
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A X YES NO

- Is it an electronic CTD? N/A X YES NO
  **If an electronic CTD, all certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Additional comments:
The sponsor submitted SAS transport files electronically

- Patent information submitted on form FDA 3542a? YES X NO

- Exclusivity requested? YES, _____3__years NO
***NOTE:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES XNO
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

***NOTE:*** *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES X NO
**(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)**

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES X NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES

- List referenced IND numbers: IND 62,261

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____April 29, 2003_____
NO
If yes, distribute minutes before filing meeting.

## Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
YES X NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES X NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A XYES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A XYES NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A XYES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  N/A YES NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES NO X
  If no, did applicant submit a complete environmental assessment? YES XNO
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES X NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO X

ATTACHMENT

## MEMO OF FILING MEETING

DATE: June 22, 2004

BACKGROUND: The initial clinical development of AMRIX was conducted under IND 62,261 for the relief of muscle spasms. The application has been filed under 505(b)(2) with a reference NDA 17-821. (Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Brian E. Harvey, M.D., Ph.D., Acting Division Director, Sharon Hertz, M.D., Deputy Director, Michael Yao, M.D., Abe Adebowale, Ph.D., Hamid Amouzadeh, Ph.D., Yongman Kim, Ph.D., Sue Ching Lin, Ph.D., Paul Z. Balcer

ASSIGNED REVIEWERS:

| **Discipline** | **Reviewer** |
|---|---|
| Medical: | Christine Fang, M.D. |
| Secondary Medical: | James P. Witter, M.D., Ph.D., Medical Team Leader |
| Statistical: | Yongman Kim, Ph.D. |
| Pharmacology: | Hamid Amouzadeh, Ph.D. |
| Statistical Pharmacology: | |
| Chemistry: | Sue Ching Lin, Ph.D. |
| Environmental Assessment (if needed): | |
| Biopharmaceutical: | Abi Adebowale, Ph.D. |
| Microbiology, sterility: | |
| Microbiology, clinical (for antimicrobial products only): | |
| DSI: | |
| Regulatory Project Management: | Paul Z. Balcer |
| Other Consults: | DMETS, DDMAC |

Per reviewers, are all parts in English or English translation? YES X NO
If no, explain:

CLINICAL FILE ___X__ REFUSE TO FILE _____

- Clinical site inspection needed: YES X NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A X YES NO

CLINICAL MICROBIOLOGY NA X_____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE __X____ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE __X____ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO X

PHARMACOLOGY NA _____ FILE _____ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE __X____ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X___ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___X___ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

____Paul Z. Balcer_____
Regulatory Project Manager, HFD-

## Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review**
**Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES X NO

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

NDA 18-271 Fexeril

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES NO X

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

   YES NO

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES **X** NO

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

Cyclobenzaprine HCl but it is not modified release.

(b) Is the approved drug product cited as the listed drug? YES **X** NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for modified release formulation of cyclobenzaprine HCl

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO **X**

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO **X**

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO X

10. Are there certifications for each of the patents listed for the listed drug(s)? N/A YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

__X__ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES X NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES X NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A YES X NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A YES NO X

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES X NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES NO X

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND # ___62,621___ NO

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

  YES X NO

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

/s/

Paul Balcer
11/22/04 05:24:51 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-777

**INFORMATION REQUEST LETTER**

ECR Pharmaceuticals

Dear [redacted]

Please refer to your April 29, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AMRIX® (cyclobenzaprine HCl) 15 and 30 mg Modified Release Capsules.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests.

1. The following information request pertains to the *drug substance*:

    a) The nonproprietary name of the drug product should be "cyclobenzaprine hydrochloride extended release capsules." The term "modified release" should not be used. Refer to Appendix C of the Orange Book for Uniform Terms.

    b) Provide detailed analytical procedures for non-compendial methods (e.g. testing related substances by HPLC), the validation of the methods, and the reference standards used in the analytical procedures.

    c) [redacted], the holder of DMF[redacted] has been requested to tighten the acceptance criteria for related substances based on the stability data of the drug substance. You are requested to revise your specification accordingly.

    d) Provide a specification sheet including a list of tests, references to analytical procedures (e.g. USP<731> for loss on drying, method number for related substances), and acceptance criteria.

2. The following information request pertains to the [redacted]

    a) Clarify whether stability is to be monitored for every batch of [redacted] that will be held for longer than [redacted] or if stability testing will only be performed when there is a post-approval change (e.g. change of drug substance supplier, process change etc.).

    b) Provide the holding time for [redacted]

3. The following information request pertains to the *drug product*:

    a) Provide a specification sheet for release and stability, including a list of tests, references to analytical procedures, and acceptance criteria. The names of the identified impurities should be listed under "single specified identified."

    b) Provide a stability protocol for annual production batches. The stability protocol should include selection of batches, storage conditions, testing frequency, and tests (with acceptance criteria)

performed. Please revise the stability protocol for the registration batches (attachment 1 in volume 8, page 23) to clearly indicate the tests and acceptance criteria (as the format shown in attachment 3, volume 8, page 77), testing frequency, and storage conditions.

c) The expiration dating period should be computed based on the date when the [redacted] are first introduced into the manufacture of the capsules, regardless of the packaging date of the capsules. Please acknowledge.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Paul Z. Balcer, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

John Smith, Ph.D.
Chemistry Team Leader for the
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, (HFD-550)
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

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/s/

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John Smith
11/17/04 07:29:19 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

# Memorandum

## Pre-Decisional Agency Information

**Date:** October 25, 2004

**To:** Paul Balcer, Regulatory Health Project Manager
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

**From:** Jialynn Wang, Pharm.D.
Iris Masucci, Pharm.D.
DDMAC, HFD-42

**Subject:** NDA 21-777
DDMAC comments on AMRIX (cyclobenzaprine HCl) draft label

DDMAC has reviewed the draft labeling for Amrix and has the following comments:

**General**

Throughout the draft PI, the sponsor frequently uses the generic name, cyclobenzaprine, in situations where use of the brand name, Amrix, may be more appropriate (i.e. situations where the final form was used in a study or within the risk information section). For example, in the PRECAUTIONS *General* section, the sponsor states, " [redacted] ." rather than, "**AMRIX** should be used with caution...." (emphasis added). Therefore, DDMAC recommends replacing all instances of "cyclobenzaprine" with "Amrix," where appropriate.

**Pharmacokinetics**

- [redacted] (emphasis added)

  DDMAC recommends deletion of the word " [redacted] because it is vague and unnecessary.

- The Flexeril label mentions that cyclobenzaprine undergoes enterohepatic recirculation and is highly bound to plasma proteins. Are these facts also applicable to the Amrix?

- The single dose pharmacokinetic results are presented in text, a figure, and a table. To avoid redundant presentations of the same information, we suggest retaining only the table, which would include all pertinent findings. We also note that the section on dosing in the elderly contains repetitive information in both text and table, when the table alone would suffice. In addition, the title for the table should clarify that this was a single dose study to differentiate it from the multiple-dose study presented later.

- *"A food effect study conducted in healthy adult subjects (n=15) utilizing a single dose of AMRIX 30 mg demonstrated a statistically significant increase in bioavailability when AMRIX 30 mg was given with food relative to the fasted state."*

  [redacted]. In general, statistics are not presented with pharmacokinetic findings. We note that "[redacted]it is also used in the section that follows on "Dosing Considerations for the Elderly."

- *"No effect, however, was noted in $T_{lag}$, $T_{max}$, or the shape of the mean plasma cyclobenzaprine concentration versus time profile."*

  Is "$T_{lag}$" a well understood pharmacokinetic parameter, or does it need explanation?

- [redacted]

**Clinical Studies**

The clinical studies section makes claims based upon measurements such as patient's rating of medication helpfulness, percent of patient responders, patient-rated relief from local pain due to muscle spasm, subject-rated restriction of movement, and patient-rated clinical global impression of change.

- We recommend consulting Laurie Burke of OND about the adequacy and validity of the evaluation of these patient-reported outcomes and which of them are appropriate for inclusion in labeling.

- For those outcomes that do remain in the label, can the rating scales be defined in more detail, e.g., scoring ranges, definitions of outcomes, etc.?

- Were Days 4, 8, and 14 predefined dates to measure response?

- As in the Pharmacokinetics section, study results are presented in both text and table unnecessarily.

- Can the "Responder Analysis" be explained more clearly? It is not clear what patient and physician assessments were included here.

**Indications and Usage**

- *"Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion,*

  Is there substantial evidence to show that Amrix provides significant improvement in each of the above outcomes? We note that the same wording appears in the Flexeril label, although it is not clear if each of these outcomes was evaluated for Amrix.

**Contraindications**

- Recommend combining bullets 2 and 3 into one bullet since bullet 3 describes the contraindication in bullet 2. This is consistent with the Flexeril PI.

- [redacted]

**Precautions**

- *"Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the*

*seizure risk in patients taking tramadol (ULTRAM® [tramadol HCl tablets, Ortho-McNeil Pharmaceutical] or ULTRACET® [tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical]).*"

Would it be more accurate to say here that "Tricyclic antidepressants, to which cyclobenzaprine is structurally similar, may block the antihypertensive action..." (emphasis added)? Also, is it necessary to include the trade names for tramadol products? Most labels do not include trade names when discussing drug interaction information.

- *"A battery of mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenic effects have provided no evidence for a mutagenic potential for cyclobenzaprine. An* in vivo *mouse bone micronucleus assay, an assessment of chromosomal aberrations (Chinese hamster ovary), and a mammalian microsome reverse mutation assay were negative."*

  Please note the above paragraph is not part of the Flexeril PI.

**Adverse Reactions**

- *"Incidence of the most common adverse reactions (occurring in ≥ 3% of subjects in any treatment group)* (emphasis added)

  As recommended in the draft guidance on the Adverse Reactions section of labeling, only those adverse events that occurred more commonly with study drug than placebo should be included in the ADR tables.

- Is the inclusion of the column on cyclobenzaprine 10 mg TID appropriate here? If the clinical results for this study arm are not included in the Clinical Studies section, does it make sense to include them in Adverse Reactions? These results could be used promotionally to portray a more favorable safety profile for Amrix vs. IR cyclobenzaprine."

- Are the postmarketing surveillance program data gathered in patients treated with cyclobenzaprine 10 mg TID applicable to Amrix patients? If not, DDMAC recommends deletion of this section.

- [redacted]

**Dosage and Administration**

- [redacted]

The Flexeril PI states, *"Less frequent dosing should be considered for hepatically impaired or elderly patients…"*

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On Original

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/s/

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Jialynn Wang
10/25/04 09:45:08 AM
DDMAC REVIEWER

NNDA 21-777CorrespondenceE-mail TO SponsorNDA21777 Submissionof120-daySafetyUpdate080504.txt
MessageFrom: Balcer, Paul
Sent: Thursday, August 05, 2004 3:08 PM
To: [redacted]
Subject: NDA 21-777 - Submission of the 120-day Safety Update

Importance: High
Sensitivity: Confidential

Dear [redacted]

Thank you for sending us an inquiry on the NDA's 120-day safety update. The following guidances should assist you in providing the information.

a.. Please submit the dataset for the ISS in SAS transport format. It should include a unique patient identifier, treatment assignment, date study started, the AE in verbatim and preferred term, date of onset (or study day at onset), date of resolution (or study day at resolution), dose at onset, intervention, if it was serious or not, concomitant meds.

a.. If possible, it would be helpful to merge all of the studies into this dataset. Otherwise, the Phase 3 studies should be integrated and the Phase 1 studies integrated.

a.. The format for the 120-day update is:

Tables with columns for original data, new data and integrated old and new data

These tables should be created for AEs. If there were only a few new SAEs, withdrawals due to AEs, or any deaths they can be reported separately.

Disposition tables and extent of exposure tables should be updated.

Sections that have absolutely nothing new can be referenced to the original submission.

a.. Please direct us to the location of the definition table in which the fields of the tables in SAS file format are defined.

a.. Safety information from literature reports should be summarized in a table in terms of source of information, study design, exposure (level/length), frequency and severity of AEs, and other important information as mentioned above.

a.. The safety experience from the immediate-release product should also be summarized and contrasted with this product.

NNDA 21-777CorrespondenceE-mail TO SponsorNDA21777 Submissionof120-daySafetyUpdate080504.txt
Please send the above information as a formal submission to the NDA. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
9201 Corporate Blvd.
Rockville, MD 20850
Phone: (301) 827 2090
Fax: (301) 827 2531
paul.balcer@fda.hhs.gov

-----Original Message-----
From: [redacted] [mailto:[redacted]
Sent: Sunday, July 25, 2004 6:06 PM
To: Paul Balcer
Subject: NDA 21-777 Request for the Medical Officer

Appears This Way
On Original

July 26, 2004

Mr. Paul Balcer
Food and Drug Administration

Consumer Safety Officer

Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, HFD 550

9201 Corporate Boulevard

Rockville, Maryland 20850

Dear Mr. Balcer

Re: ECR Pharmaceuticals

NNDA 21-777CorrespondenceE-mail TO SponsorNDA21777 Submissionof120-daySafetyUpdate080504.txt

NDA 21-777

Product: Amrix (Cyclobenzaprine Modified Release Capsules)

Our current intent is to file the 120 Day Safety Update using the ISS TOC as the backbone of the submission. I believe we currently have two normal pregnancies to add to the ISS.

1. Could you check with the Medical Officer if this would be sufficient in content for the 120 Day Safety Update?

2. Would the Medical Officer prefer we only update the sections and tables which would be affected by the two new AEs and then cross reference the other sections to the original ISS submission contained in the NDA or would he/she prefer we also keep the material that is unaffected by the new data in the Updated ISS?

3. Lastly, would the agency want us to perform a safety literature search for previously unreported events pertaining to safety for the IR product from the date of the material covered in the original NDA up to the end of July? (Planned Submission-mid September)? There should be no CMR studies to report on.

Thank you for your time and assistance on these issues.

Best regards,

[redacted]

Email: [redacted]

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/s/

Paul Balcer
2/15/05 04:54:03 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# REQUEST FOR CONSULTATION

TO (Division/Office):
**Mail: Jailynn Wang, OMP/DDMAC (HFD-042)**

FROM: Paul Z. Balcer, Regulatory Health Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| July 28, 2004 | N/A | 21-777 | Original Application | April 30, 2004 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| AMRIX (cyclobenzaprine HCl) | S | 5030310 | September 27, 2004 |

NAME OF FIRM: ECR Pharmaceuticals

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

  Labeling Review

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

**COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:**

**PDUFA DATE: 28 February 2005**
**ATTACHMENTS:** Draft Package Insert, Container and Carton Labels
**CC:**
Archival IND/NDA 21-777
HFD-550/Division File
HFD-550/RPM
HFD-550/Reviewers and Team Leaders

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) |
|---|---|
| Carmen DeBellas, CPMS | ☐ MAIL ☒ E-MAIL ☐ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

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/s/

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Carmen DeBellas
7/28/04 06:08:42 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# REQUEST FOR CONSULTATION

TO *(Division/Office)*:
**Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 PKLN Rm. 6-34**

FROM: Paul Z. Balcer, Regulatory Health Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT: | DATE OF DOCUMENT |
|---|---|---|---|---|
| July 28, 2004 | N/A | 21-777 | Original Application | April 30, 2004 |

| NAME OF DRUG | PRIORITY CONSIDERATION: | CLASSIFICATION OF DRUG: | DESIRED COMPLETION DATE: |
|---|---|---|---|
| AMRIX (cyclobenzaprine HCl) | S | 5030310 | September 27, 2004 |

NAME OF FIRM: ECR Pharmaceuticals

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

**COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:**

**PDUFA DATE: 28 February 2005**
**ATTACHMENTS:** Draft Package Insert, Container and Carton Labels
**CC:**
Archival IND/NDA 21-777
HFD-550/Division File
HFD-550/RPM
HFD-550/Reviewers and Team Leaders

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) |
|---|---|
| Carmen DeBellas, CPMS | ☐ MAIL ☒ E-MAIL ☐ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

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/s/

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Carmen DeBellas
7/28/04 02:42:18 PM

NNDA 21-777CorrespondenceE-mail TO SponsorNDA21777120-daysafetyupdatequestion072104.txt
MessageFrom: Balcer, Paul
Sent: Wednesday, July 21, 2004 3:04 PM
To: [redacted]
Cc: DeBellas, Carmen; Fang, Christina L
Subject: RE: NDA 21-777 AMRIX (cyclobencaprine HCl) - 120-day safety update question

Sensitivity: Confidential

Dear [redacted]

Thank you for leaving me the voice mail with the information about the mailing of the labeling. In regards to the 120-day safety update, yes the ISS needs to be updated with any AEs, since the submission of the NDA. Please send the information to CDERs' address.

If you have any further questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
9201 Corporate Blvd.
Rockville, MD 20850
Phone: (301) 827 2090
Fax: (301) 827 2531
paul.balcer@fda.hhs.gov

-----Original Message-----
From: [redacted] [mailto:[redacted]
Sent: Tuesday, July 20, 2004 3:51 PM
To: 'Balcer, Paul'
Cc: 'DeBellas, Carmen'
Subject: RE: NDA 21-777 AMRIX (cyclobencaprine HCl) - Request for the MS W ord version of package insert and carton labeling-Response.
Sensitivity: Confidential

Paul

I forgot to put that on the mail. I will send it out again tomorrow. I tried to get the secure e-mail account but I have the newest version of Outlook and of course the directions from Verisign don't work to attach the e-mail signature. I am playing with it to try and get it to work .It is probably all part of the Bill Gates conspiracy. Update the product so it doesn't work with existing applications forcing vendors to develop more and probably paying Bill a tidy sum for his help in making their application work.

Best regards,

[redacted]

[redacted]

NNDA 21-777CorrespondenceE-mail TO SponsorNDA21777120-daysafetyupdatequestion072104.txt

-----Original Message-----
From: Balcer, Paul [mailto:BalcerP@cder.fda.gov]
Sent: Tuesday, July 20, 2004 1:30 PM
To: [redacted]
Cc: DeBellas, Carmen
Subject: RE: NDA 21-777 AMRIX (cyclobencaprine HCl) - Request for the MS W ord version of package insert and carton labeling.
Sensitivity: Confidential

[redacted]

I got your VM. Thank you for sending me the diskette. Please make sure that you include the words "DESK COPY" on the package labeling, so the mailing is not processed through the document room.

Regards,

Paul Z. Balcer

Regulatory Health Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

9201 Corporate Blvd.

Rockville, MD 20850

Phone: (301) 827 2090

Fax: (301) 827 2531

paul.balcer@fda.hhs.gov

-----Original Message-----
From: [redacted] [mailto: [redacted]]
Sent: Tuesday, July 20, 2004 1:00 PM
To: 'Balcer, Paul'
Cc: 'DeBellas, Carmen'
Subject: RE: NDA 21-777 AMRIX (cyclobencaprine HCl) - Request for the MS W ord version of package insert and carton labeling.
Sensitivity: Confidential

Dear Paul

The files you requested have been mailed on a diskette and should be at the Agency by noon on the 21st. I mailed them directly to you as you had requested that the other electronic files be sent that way.

Best regards,

-----Original Message-----
From: Balcer, Paul [mailto:BalcerP@cder.fda.gov]
Sent: Monday, July 19, 2004 11:28 AM
To: [redacted]
Cc: DeBellas, Carmen
Subject: RE: NDA 21-777 AMRIX (cyclobencaprine HCl) - Request for the MS W ord version of package insert and carton labeling.
Importance: High
Sensitivity: Confidential

Dear [redacted]

Thank you for sending me two CD ROMs with SAS Files Descriptions, Study Reports, Protocols and Labeling. Unfortunately, I have received a PDF version of the carton labeling only. We need for review the

MS Word version of the proposed package insert and carton labeling.

Please provide both as soon as possible.

Regards,

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Paul Z. Balcer

Regulatory Health Project Manager

Food and Drug Administration

NNDA 21-777CorrespondenceE-mail TO SponsorNDA21777120-daysafetyupdatequestion072104.txt

Dear [redacted]:

The Division of the Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP) held a filing meeting to discuss the above NDA. The reviewers request the following:

1. electronic SAS database transport files
2. electronic version of the protocol (MS Word Version)
3. electronic version of the proposed labeling (MS WORD version)

To assist you and your client in providing the above documentation, please refer to:

1. Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs
2. Guidance for Industry Providing Regulatory Submissions in Electronic Format -General Considerations

both guidances are attached.

Please provide the above files as soon as possible, but no later than July 9, 2004.

You may also want to establish secure e-mail with the FDA, by contacting Wendy Lee, the FDA E-mail Administrator at leew@cder.fda.gov

If you have further questions, please contact me.

Regards,

Paul Z. Balcer

Regulatory Health Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

9201 Corporate Blvd.

Rockville, MD 20850

Phone: (301) 827 2090

Fax: (301) 827 2531

paul.balcer@fda.hhs.gov

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/s/
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Paul Balcer
2/25/05 07:40:08 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-777

ECR Pharmaceuticals

Dear

Please refer to your April 29, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AMRIX® (cyclobenzaprine HCl), 15 and 30 mg modified release capsules.

We also refer to your submissions dated May 7, 9 and 27, 2004, June 29, 2004 and July 6, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 29, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Paul Z. Balcer, Regulatory Project Manager, at (301) 827 2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

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Carmen DeBellas
7/13/04 11:18:47 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-777

ECR Pharmaceuticals

Dear [redacted]

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

| | |
|---|---|
| Name of Drug Product: | AMRIX®, (cyclobenzaprine HCl), 15, 30 mg modified-release capsules. |
| Review Priority Classification: | Standard (S) |
| Date of Application: | April 29, 2004 |
| Date of Receipt: | April 30, 2004 |
| Our Reference Number: | NDA 21-777 |

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Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 29, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 28, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room, N115
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room, N115
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Paul Z. Balcer, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/
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Carmen DeBellas
7/7/04 04:03:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

# PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

***See Instructions on Reverse Side Before Completing This Form***

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
E. Claiborne Robins Company, Inc.
DBA ECR Pharmaceuticals
3969 Deep Rock Road
Richmond, Virginia 23233

2. TELEPHONE NUMBER *(Include Area Code)*
( 804 ) 527-1950

3. PRODUCT NAME
AMRIX (cyclobenzaprine HCl modified release capsules)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-777

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☒ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
*(See item 8, reverse side if answered YES)*

**Public reporting burden for this collection of information** is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE | TITLE | DATE |
|---|---|---|
| Wars S. Cooley | Vice President, Pharmaceutical Operations | 4/29/2004 |

**MEETING DATE:** October 3, 2001 **TIME:** 1:00 pm **LOCATION:** CORP S300

IND 62,261

**Meeting Request Submission Date:** August 8, 2001
**Meeting Package submitted:** August 31, 2001

# MEETING MINUTES

**DRUG:** Cyclobenzaprine HCl modified release capsules

**APPLICANT:** ECR Pharmaceuticals

**TYPE of MEETING:** A type B meeting to discuss the development of the modified release cyclobenzaprine HCl

**FDA PARTICIPANTS:**

| | |
|---|---|
| Jonca Bull, M.D. | Acting Division Director, DAAODP |
| Dennis Bashaw, Pharm.D. | Biopharmaceutics Team Leader |
| Mary jane Walling | Project Manager |
| Lourdes Villalba, M.D. | Clinical |
| Jame Witter, M.D., Ph.D. | Clinical |
| Joel Schiffenbauer, M.D. | Clinical |
| Carmen DeBellas | Project manager |
| Jyoti Zalkikar | Statistics |

**INDUSTRY PARTICIPANTS:**



| | |
|---|---|
| Gopi Venkatesh, Ph.D. | Product Development |
| James Harper, Ph.D. | Biometrics |
| Robert Ferraino | V.P. Regulatory |
| Laura Fantauzzi | Regulatory |
| Robert Murphy | ECR V.P. |

The following overheads were provided by FDA in response to the sponsor's pre-meeting package questions:

**Responses to Question 1.**

a- Please define what is meant by "major". If it assumed that it would be the pivotal study, then it will not satisfy the requirement for the clinical studie(s).

- Entry criteria

- Protocol should define duration of muscle spasm prior to study entry (• 7 days).
- Physician examination should confirm the presence of muscle spasm.

- Endpoints

- In addition to the proposed endpoint (Patient overall assessment of response at the end of the study), other endpoints such as Patient rating of medication helpfulness and Relief from starting pain due to muscle spasm should be included as primary variables.

- Since this product would be indicated for the relief of muscle spasm associated with acute musculoskeletal conditions, in addition to the end of study analyses, primary efficacy parameters should also be analyzed at earlier time points.

- It is not clear how will the patients complete baseline assessment of the primary efficacy variable and some of the proposed secondary variables on day 1.

- The duration of treatment may not be a meaningful endpoint unless the distinction is made between patients who discontinue due to complete relief from pain due to muscle spasm and those who discontinue due to lack of efficacy and/or adverse events. If this distinction is not made, the statistical results on this endpoint will not be interpretable for efficacy evaluation. The data on the duration of treatment should be analyzed using survival analysis methods outlined clearly in the protocol.

- Time to improvement would provide relevant information about onset of action. It should be confirmed by at least one later measurement.

- Concomitant treatment

- Analgesics and NSAIDs should preferably not be allowed during the protocol. Protocol should specify that topical pharmacologic therapy is not allowed (e.g. Ben-gay, capsaicin). Initiation of physical therapy should not be allowed during the protocol.

- An arm with 10 mg of Flexeril® tid should be added to the proposed study.

- Duration of the proposed study appears to be short. Label would reflect available data.

b- Two clinical studies will be required. The PK study will not suffice as an additional clinical trial for safety and efficacy.

**Responses to Question 2**

The sample size and the analyses will depend on the endpoints agreed upon. Study 1105 does not appear to be sufficient. The sponsor should provide the details about the assumptions made in sample size and power calculations based on those endpoints.

**Responses to Question 3**

The proposed trial is acceptable but not in itself sufficient to satisfy all of the biopharm requirements.

**Additional comments:**

- The Division is concerned with the safety profile of cyclobenzaprine 30 mg once daily, particularly in the elderly.

- The sponsor should address the potential for dependence, withdrawal and abuse of this new formulation.

In addition to the responses provided in FDA overheads, the following points were part of the discussion:

The determination of the "pivotal" nature of the clinical studies will be part of the determination by the FDA as to the suitability of applying for 505(b)(2) status.

There was a discussion of endpoints. It would be desirable to characterize the time to response. Perhaps the 2-week response measurement is not as meaningful as 3 days, since this is an acute condition. Three days would be acceptable. Twenty-four hours may be even better. Response at two weeks would be confirmatory.

The sponsor clarified that the patient response time is compared to patient baseline rating. Further clarifications for the FDA statistical reviewer included a request for data to distinguish between drop out for ADEs or lack of efficacy or efficacy resulting in requiring no further treatment

The preference would be for no allowance for use of concomitant medications, but if allowed, should be recorded, tabulated and analyzed. PT is acceptable as long as it is not started during the trial.

It is unlikely that a single trial will provide all the needed information. The original NDA application for cyclobenzaprine does not contain all the data that FDA would require for approval today (particularly PK and safety data, e.g. safety in the elderly, potential for abuse).

The division recommended 2 trials with each including Flexeril, placebo, and 30 mg of the ECR modified release product.

A small number of naï ve elderly patients should be studied prior to approval.

**ACTION ITEMS:**

1. A separate CMC meeting will be arranged at the time of the pre NDA meeting.
2. The sponsor will submit a proposal for a clinical study protocol.
3. The division will have internal discussions with Office of Generic Drugs about 505(b)(2) status.
4. The sponsor will send literature and marketing information about the use of the drug worldwide.
5. A telecon will be scheduled with Dr. Bashaw and the sponsor to discuss in detail the protocols, the mean absorption rates and dissolution methodology.

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MJ Walling
Project Manager

Concur:_____
Jonca Bull, M.D.
Acting Division Director, DAAODP

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