CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-777

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-777

ECR Pharmaceuticals
c/o [redacted]
Attention: [redacted]
[redacted]
[redacted]
[redacted]

Dear [redacted]

Please refer to your new drug application (NDA) dated April 29, 2004, received April 30, 2004, 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 acknowledge receipt of your submissions dated June 29, July 20, and 30, August 30, October 4, December 10, 17 and 23, 2004, January 22 and 29, and February 16, 2005.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies:

Deficiencies:

1. The clinical trials submitted to support a finding of efficacy did not provide adequate evidence of efficacy. Neither Study 1105, nor Study 1106 met the prespecified criteria for a demonstration of efficacy for either the 15 mg or 30 mg doses of Amrix.

2. As a 505(b)(2) application, reliance of prior findings of safety for this application were predicated on similar exposure for Amrix and the reference listed product under conditions of use. However, comparable bioavailability between Amrix and the reference listed product has not been demonstrated for either the initial single-day dosing or steady state. The data suggest that the bioavailability of Amrix may be greater than that of the reference listed product.

3. The half life of Amrix in the elderly is substantially prolonged compared to younger subjects. The pharmacokinetic characteristics of Amrix were not evaluated in patients with hepatic insufficiency, although it is known from the reference listed product that patients with hepatic insufficiency have increased exposure to cyclobenzaprine. The proposed dosing recommendations for elderly patients and for patients with impaired hepatic function are not adequate to ensure safe use in these populations.

4. The dissolution acceptance criteria are too wide to ensure consistent batch to batch quality.

5. Risks associated with the use of cyclobenzaprine include inadvertent and intentional overdose. As this new formulation represents a large dose per dosing unit, with a prolonged half life, risk is greater, particularly for inadvertent overdose. The proposed

Information needed to address the Deficiencies:

1. Provide evidence of efficacy in at least one adequate and well-controlled study in the intended population, in which substantial evidence of efficacy for the cyclobenzaprine hydrochloride extended-release 15 mg and 30 mg doses with evidence of a dose-response effect could be sufficient to register the two doses.

2. To address whether there are additional safety concerns with the Amrix formulation, either demonstrate sufficiently similar relative bioavailability to the reference listed product to address these concerns or provide an adequately sized safety database by conducting clinical trials of sufficient size and duration in the target population.

3. Provide directions for use in the elderly and in patients with hepatic insufficiency that offer adequate safeguards for these populations.

4. Revise the proposed dissolution acceptance criteria for the 4-hr and 8-hr sampling time point. Based on the dissolution data, the proposed acceptance criteria at the 4-hr and 8-hr time points should be tightened to 4-hr = — % and 8-hr = — %, to ensure consistent batch to batch quality.

5.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

8. The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper.

In addition, as required by 21 CFR 314.550, please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the proposed package insert directly to:

Division of Drug Marketing, Advertising
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file (an) amendment(s), or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Paul Z. Balcer, Regulatory Project Manager, at (301) 827 2504.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: Davis S. Caskey, Vice President, Pharmaceutical Operations

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/s/

Sharon Hertz
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