DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-710

Zohra Lomri, M.S.
Senior Manager, Regulatory Affairs
Shire Development, Inc.
725 Chester Brook Boulevard
Wayne PA 19087

Dear Ms. Lomri:

Please refer to your new drug application (NDA) dated February 13, 2004, received February 13, 2004, and submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for EQUETRO (carbamazepine) extended-release capsules 100 mg, 200 mg, and 300 mg.

We acknowledge receipt of your additional submissions dated February 13, 2004, February 19, 2004, March 8, 2004, March 12, 2004, May 10, 2004, October 6, 2004, October 20, 2004, October 26, 2004, October 27, 2004, November 3, 2004, November 8, 2004, November 17, 2004, and December 6, 2004 (via secure e-mail).

This new drug application provides for the use of EQUETRO (carbamazepine) extended-release capsules 100 mg, 200 mg, and 300 mg as monotherapy in the acute treatment of manic or mixed symptoms associated with Bipolar I Disorder.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text attached to this letter. Your proposed proprietary name, EQUETRO, has been reviewed and found acceptable by the Agency.

OCPB and CMC:
Approved Dissolution Specification and Expiration Date, Methods Validation, Categorical Exclusion
Approval of this application includes the following dissolution specification and method, to be used for all three approved capsule strengths:

	(b)(4)
Apparatus:	
Media:	
Specifications:	

The approved expiration date for the drug product is 24 months (all strengths, all package configurations).

We have waived the requirement for validation of the regulatory methods, based on their identity to those already approved for Carbatrol.

We note your request for categorical exclusion from the environmental assessment requirements, as per 21 CFR 25.31(b). We have reviewed this request, and it has been found acceptable.

Pediatric Research Equity Act (PREA) Requirements: Phase 4 Commitment: Studies Deferred
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 are waiving studies for ages 0 to 10 years (neonates and children). We are deferring submission of your pediatric studies for ages 10 to 17 years (children and adolescents) until January 30, 2009 (see below).

Your deferred pediatric study required under Section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of such postmarketing commitments shall be reported annually according to 21 CFR 314.81. The associated commitment is listed below.

1. *Deferred pediatric studies under PREA*
   You are required to assess the safety and effectiveness of EQUETRO as a treatment for acute manic and mixed episodes associated with Bipolar I Disorder in pediatric patients ages 10 to 17 (children and adolescents). Due to extensive prior experience with carbamazepine in the treatment of pediatric epilepsy, we do not require either a pediatric pharmacokinetic study or a juvenile animal toxicity study to support this pediatric study.

   Final Report Submission: January 30, 2009

Please submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment, whether submitted to the IND or the NDA, must be clearly designated "**Required Pediatric Study Commitments**".

Pediatric Exclusivity
Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request" ***in addition to*** your plans for pediatric drug development described above. Please note that satisfaction of the requirements in Section 2 of PREA alone may not qualify you for pediatric exclusivity.

Additional Phase 4 Commitments (by Discipline)
We remind you of your additional postmarketing commitments, agreed upon as of December 6 and December 7, 2004. These commitments are listed below.

2. *Educational Campaign to Educate Practitioners and Patients Concerning the Identical Active Ingredients in both EQUETRO and CARBATROL.*
   You have agreed to assure differentiation in packaging between EQUETRO (carbamazepine) extended-release capsules and your approved drug CARBATROL®; this is an ongoing commitment, with no specific time limit. You have also agreed to institute an educational campaign that will educate practitioners and patients concerning the identical active ingredient in both EQUETRO and CARBATROL.

   Educational Campaign Materials Submission: On or before March 31, 2005.

3. *Clinical Efficacy: Adult clinical study to address longer-term effectiveness of carbamazepine in Bipolar I Disorder.*
   You have agreed to submit the results of one adult clinical study of carbamazepine in the longer-term treatment of Bipolar I Disorder.

   Final Report Submission: On or before August 30, 2009.

Please submit clinical protocols to your IND for this product. Submit final study reports to this NDA, including any final reports intended to support clinical efficacy claims or changes in labeling. Please submit the educational campaign materials requested under point 2. above to this NDA.

In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary for each commitment in your annual report to this NDA. The status summary should include

- expected final report submission dates,
- any changes in plans since the last annual report,
- and, for clinical studies, the number of patients entered into each study.

All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Phase 4 Commitment Postmarketing Study Protocol**", "**Phase 4 Commitment Postmarketing Study Final Report**", or "**Phase 4 Commitment Postmarketing Study Correspondence**."

Labeling
The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling (text for the package insert) and to the container, carton, and blister labeling in your submission of December 6, 2004, with modifications as agreed to on December 9, 2004. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We note your agreement to place only the nonproprietary drug name, carbamazepine, in parentheses, and to include the statement "Protect from light." in the storage instructions. These agreements will apply to the package insert and to all trade dress and physician sample bottle labels [FAXes from Shire to CMC review team, November 3 and November 8, 2004].

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

submission "**FPL for approved NDA 21-710**." Approval of this submission by FDA is not required before the labeling is used.

Introductory Promotional Materials
In addition, 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 package insert(s) directly to:

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

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}
Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of New Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling (package insert only, clean copy)

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

/s/

Russell Katz

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