DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-873/S-018

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ms. Kelly S. Billingham
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Billingham:

Please refer to your supplemental new drug application dated January 31, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mexitil (mexiletine hydrochloride) Capsules, 150, 200 and 250 mg.

We acknowledge receipt of your submission dated September 2, 2003, which constituted a complete response to our October 29, 2002 action letter.

This supplemental new drug application provides for final printed labeling revised as follows:

1. Under **DESCRIPTION**, the third paragraph has been changed from:

   Mexitil capsules contain the following inactive ingredients: colloidal silicon dioxide, corn starch, magnesium stearate, titanium dioxide, gelatin, FD&C Red No. 40, D&C Red No. 28 and FD&C Blue No. 1; the Mexitil 150 mg and 250 mg capsule also contain FD&C Yellow No. 10. Mexitil capsules may contain one or more of the following components: sodium lauryl sulfate, sodium proprionate, edetate calcium disodium, benzyl alcohol, carboxymethylcellulose sodium, glycerin, butylparaben, propylparaben, methylparaben, pharmaceutical glaze, ethylene glycol monoethylether, soya lecithin, dimethylpolysiloxane, refined shellac (food grade) and other inactive ingredients.

   To:

   MEXITIL capsules contain the following excipients: colloidal silicon dioxide, corn starch, magnesium stearate, titanium dioxide, gelatin, pharmaceutical glaze, simethicone, FD&C Red No. 40, and FD&C Blue No. 1; the MEXITIL 150 mg and 250 mg capsules also contain FD&C Yellow No. 10 and D&C Red No. 28. MEXITIL capsules may contain one or more of the following components: sodium lauryl sulfate, lecithin, shellac, and FD&C Blue No. 1 Aluminum Lake.

2. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the fifth sentence has been changed from:

   Mexitil is metabolized in the liver.

   To:

   MEXITIL is mainly metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. With involvement of CYP2D6, there can be either poor or extensive

metabolizer phenotypes. Since approximately 90% of MEXITIL is metabolized in the liver into inactive metabolites, pathological changes in the liver can restrict hepatic clearance of MEXITIL and its metabolites. The metabolic degradation proceeds via various pathways including aromatic and aliphatic hydroxylation, dealkylation, deamination and N-oxidation. Several of the resulting metabolites are submitted to further conjugation with glucuronic acid (phase II metabolism); among these are the major metabolites p-hydroxymexiletine, hydroxy-methylmexiletine and N-hydroxy-mexiletine.

3. Under **PRECAUTIONS/Drug Interactions**, the following has been added as the first paragraph:

   Since MEXITIL is a substrate for the metabolic pathways involving CYP2D6 and CYP1A2 enzymes, inhibition or induction of either of these enzymes would be expected to alter mexiletine plasma concentrations. In a formal, single-dose interaction study (n = 6 males) the clearance of mexiletine was decreased by 38% following the coadministration of fluvoxamine, an inhibitor of CYP1A2. In another formal study (n = 8 extensive and n = 7 poor metabolizers of CYP2D6), coadministration of propafenone did not alter the kinetics of mexiletine in the poor CYP2D6 metabolizer group. However, the metabolic clearance of mexiletine in the extensive metabolizer phenotype decreased by about 70% making the poor and extensive metabolizer groups indistinguishable. In this crossover steady state study, the pharmacokinetics of propafenone were unaffected in either phenotype by the coadministration of mexiletine. Addition of mexiletine to propafenone did not lead to further electrocardiographic parameters changes of QRS, QTc, RR, and PR intervals than propafenone alone. When concomitant administration of either of these two drugs is initiated, the dose of mexiletine should be slowly titrated to desired effect.

4. Under **Hematology**, the first sentence of the third paragraph has been changed from:

   In post-marketing experience, there have been isolated, spontaneous reports of pulmonary changes including pulmonary fibrosis during Mexitil therapy with or without other drugs or diseases that are known to produce pulmonary toxicity.

   To:

   In post-marketing experience, there have been isolated, spontaneous reports of pulmonary changes including pulmonary infiltration and pulmonary fibrosis during MEXITIL therapy with or without other drugs or diseases that are known to produce pulmonary toxicity.

5. Under **Hematology**, the third sentence of the third paragraph has been changed from:

   In addition, there have been isolated reports of exacerbation of congestive heart failure in patients with pre-existing compromised ventricular function.

   To:

   In addition, there have been isolated reports of drowsiness, nystagmus, ataxia, dyspepsia, hypersensitivity reaction, and exacerbation of congestive heart failure in patients with pre-existing compromised ventricular function.

6. Under **OVERDOSAGE**, the first sentence has been changed from:

   Clinical findings associated with Mexitil overdosage have included nausea, hypotension, sinus bradycardia, parasthesia, seizures, bundle branch block, AV heart block, asystole, ventricular tachyarrhythmia, including ventricular fibrillation, cardiovascular collapse and coma.

   To:

Clinical findings associated with MEXITIL overdosage have included drowsiness, confusion, nausea, hypotension, sinus bradycardia, parasthesia, seizures, bundle branch block, AV heart block, asystole, ventricular tachyarrhythmia, including ventricular fibrillation, cardiovascular collapse and coma.

7. Under **HOW SUPPLIED**, the first paragraph has been changed from:

   Mexitil (mexiletine hydrochloride, USP) is supplied in hard gelatin capsules containing 150 mg, 200 mg or 250 mg of mexiletine hydrochloride:

   To:

   MEXITIL (mexiletine hydrochloride, USP) is supplied in bottles of 100 hard gelatin capsules containing 150 mg, 200 mg or 250 mg of mexiletine hydrochloride:

8. Under **HOW SUPPLIED**, the phrase "Available in bottles of 100" has been removed from the second, third and forth paragraphs, which describe the individual dosages. The phrase "bottles of 100", which was added to the first paragraph, now applies to each of the individual dosage descriptions that follow.

9. Under **HOW SUPPLIED**, the fifth paragraph has been changed from:

   Store at controlled room temperature 20-25° C (68-77° F).

   To:

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

10. Editorial Changes:

    a. Under **ADVERSE REACTIONS**, the two tables shown are now labeled as Table 1 and Table 2, and referenced as such in the text.
    b. Throughout, Mexitil has been changed to MEXITIL or MEXITIL (mexiletine hydrochloride, USP).
    c. Notation of Copyright is included.
    d. US Patent information has been deleted.

We have completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on September 2, 2003.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doug Throckmorton

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