CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74865

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 74-865 DRUG PRODUCT: Mexiletine Hydrochloride

M:Danbury Pharmacal, Inc. DOSAGE FORM: Capsule

STRENGTHS: 150 mg, 200 mg and 250 mg

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP certification is satisfactory (See Page 1957).

EIR update : Acceptable EER pending.

BIO STUDY: Satisfactory.
Bio.study reviewed by M. Park on 6-28-96 and found acceptable. See acceptable letter on 7-5-96.

Bio. dissolution specification : NLT Q) in 30 minutes.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Compendial drug substance and drug product no samples or validation by FDA required. Laboratory may certify product meets compendial standards.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
Containers used in the stability testing are the same as described in the container section.

r 150 mg,200 mg and 250 mg capsules :
.e summary of container/closure system :

For 150 mg capsules, 100's:
Container: 100 cc HDPE

For 150 mg capsules, 500's:
Container: 400 cc HDPE

For 150 mg capsules, 1000's:
Container: 750 cc HDPE

For 200 mg capsules, 100's:
Container: 120 cc HDPE

For 200 mg capsules, 500's:
Container: 500 cc HDPE

For 200 mg capsules, 1000's:
Container: 950 cc HDPE

For 250 mg capsules, 100's:
Container: 150 cc HDPE

For 250 mg capsules, 500's:
Container: 625 cc HDPE

For 250 mg capsules, 1000's:
Container: 1250 cc HDPE

LABELING:
Satisfactory per A.Vezza on 2-2-98.

STERILIZATION VALIDATION (IF APPLICABLE):
NA

E OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Mexiletine Hydrochlorie capsules, 250 mg lot #09520C is compared to the listed drug Mexitil Capsules; Boehringer Ingelheim.(lot# 682001A). A waiver of invivo bioavailability testing for the 150 mg and 200 mg lot# 09999C and 09998C) capsules was requested and granted.

The size of the bio batch was
capsules 250 mg(lot #09520C).
Firm's source of NDS OK : 2-3-98. Adequate

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

For 150 mg capsules: capsules, lot # 09999C.
For 200 mg capsules: capsules,lot # 09998C.
For 250 mg capsules: capsules,lot # 09520C.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

For 150 mg capsules: capsules.
For 200 mg capsules: capsules.
For 250 mg capsules: capsules.

Manufacturing process is the same as biostability batch.

CHEMIST: S. Basaran DATE:2-3-1998

Team Leader: U.Venkataram DATE:2-19-1998

2/23/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74865

CORRESPONDENCE

Danbury Pharmacal, Inc.
131 West Street
Danbury, CT 06810

Tel. 203 744-7200
Fax 203 798-6161

SCHEIN PHARMACEUTICAL

October 10, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Major Amendment

Reference: Mexiletine Hydrochloride Capsules, USP, 150 mg, 200 mg and 250 mg
ANDA 74-865

Dear Sir/Madam:

This is in reference to your letter of August 27, 1996 regarding our pending ANDA 74-865 for Mexiletine Hydrochloride Capsules, USP, 150 mg, 200 mg and 250 mg submitted on February 29, 1996. Danbury Pharmacal, Inc. (DPI) is amending the application to provide for the following in response to the Agency's August 27, 1996 correspondence:

A. Chemistry Deficiencies

PAGES 2-9 REDACTED AS CHEMISTRY DEFICIENCIES

B. **Labeling Deficiencies**

The container labels and package insert labeling have been revised according to your comments and final printed copies are supplied in **Exhibits XIX** and **XX**, respectively.

A side-by-side comparison of our presently proposed labeling with that of our last submission, with the differences annotated, is provided in **Exhibit XXI**.

C. **Other**

1. We note and acknowledge that the USP 23/NF 18 was effective January 1, 1995. The specifications and test methods for the drug substance and drug product comply with USP 23/NF 18 requirements.

Please contact the undersigned at (914) 278-3742 or by fax at (914) 278-3741 if you have any questions regarding this submission.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this submission has been provided to the Food and Drug Administration New England District Office in Stoneham, Massachusetts.

Sincerely,

William R. McIntyre

William R. McIntyre, Ph.D.
Vice President
Regulatory and Professional Affairs

cc: Director, Buffalo District Office (cover letter)

ANDA 74-865

Danbury Pharmacal, Inc.
Attention: William R. McIntyre, Ph.D.
131 West Street
Danbury, CT 06810

AUG 27 1996

Dear Dr. McIntyre:

This is in reference to your abbreviated new drug application dated February 29, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Mexiletine Hydrochloride Capsules USP, 150 mg, 200 mg, and 250 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

PAGES 2 and 3 REDACTED

CMC

B. Labeling Deficiencies

1. CONTAINER: 100s and 500s (150 mg, 200 mg, 250 mg)

   a. Relocate the statement, **"TAKE WITH FOOD OR ANTACID"**, to the front panel beneath the capsule strength. Print the statement in upper case bold print.

b. Increase the prominence of the text printed on the side panel.

c. Revise "Dosage" to read "Usual Dosage".

d. Revise your storage temperature statement to read, "Store at controlled room temperature 20-25°C (68-77°F)".

2. INSERT

a. GENERAL COMMENTS

i. Delete the terminal zero following a decimal point except within the tables. Please revise accordingly throughout the insert.

ii. Add the word "hydrochloride" to the following places:

A) CLINICAL PHARMACOLOGY
Electrophysiology in Man:
- last paragraph, second sentence
Hemodynamics:
- first sentence

B) PRECAUTIONS
General:
- last paragraph, first sentence

C) DOSAGE AND ADMINISTRATION
- first paragraph, second sentence
- last paragraph, first sentence
Transferring to Mexiletine
- Revise the subsection heading to read, "Transferring to Mexiletine hydrochloride".
- paragraph one, two occurrences
- last paragraph, first sentence

b. DESCRIPTION

i. In the first sentence of the first paragraph replace "and 250 mg" with "or 250 mg".

ii. Penultimate paragraph -

Revise to read:

Each capsule, for oral administration, contains 150 mg, 200 mg, or 250 mg mexiletine hydrochloride. In addition, each capsule contains the following inactive ...

iii. We note you have not listed the components of the imprinting inks in your list of inactive ingredients. Please include pharmaceutical glaze, propylene glycol and the dyes of the imprinting inks.

c. WARNINGS

Revise this section to appear as follows:

WARNINGS

Mortality: In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicentered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3.0%). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain. Considering the known proarrhythmic properties of mexiletine and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of mexiletine as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmia.

Acute Liver Injury: In postmarketing...

d. PRECAUTIONS (Pediatric Use)

... in the pediatric population have ...

e. ADVERSE REACTIONS

i. In the first table under "Placebo N=49" revise the adverse events for "Changes in Sleep Habits" to read "16.3" rather than "6.3".

ii. Add the following sentence as the last sentence of this section:

... function. There have been rare reports of pancreatitis associated with mexiletine treatment.

f. OVERDOSAGE

Revise this section to read as follows:

Clinical findings associated with mexiletine overdosage have included nausea, hypotension, sinus bradycardia, paresthesia, seizures, bundle branch block, AV heart block, asystole, ventricular tachyarrythmia, including ventricular fibrillation, cardiovascular collapse and coma. The lowest known dose in a fatality case was 4.4 g with postmortem serum mexiletine level of 34-37 mcg/mL (Jequier P. et al. Lancet 1976: 1 (7956): 429). Patients have recovered from ingestion of 4 g to 18 g of mexiletine (Frank S. E. et al. Am J Emerg Med 1991: 9:43-48).

There is no specific antidote for mexiletine. Management of mexiletine overdosage includes general supportive measures, close observation and monitoring of vital signs. In addition, the use of pharmacologic interventions (e.g., pressor agents, atropine or anticonvulsants) or transvenous cardiac pacing is suggested, depending on the patient's clinical condition.

g. HOW SUPPLIED

i. We note you have indicated in your list of components that your capsule shells are imprinted. Please list each capsule imprint following their color description.

ii. See comment 1(d) under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit in final print. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission and in accordance with 21 CFR 314.94(a)(8)(ii), please provide a side-by-side comparison of your proposed labeling with your last submission.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

> The USP 23/NF 18 was effective January 1, 1995. The specifications and test methods for drug substance and drug product should be updated to comply with USP 23/NF 18 requirements.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

for 8/27/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-865

Danbury Pharmacal, Inc.
Attention: William R. McIntyre, Ph.D.
131 West Street
Danbury, CT 06810

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Mexiletine Hydrochloride Capsules USP, 150 mg, 200 mg, and 250 mg

DATE OF APPLICATION: February 29, 1996

DATE OF RECEIPT: March 4, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Timothy Ames
Project Manager
(301) 594-1841

Sincerely yours,

3/18/96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-865
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSF _____ date
HFD-615/WRussell, CSO _____ date
HFD-647/JSimmons, Sup Chem 3-15-96 date
File\x:\new\firmsam\Danbury\ltrs&rev\74865ac.f
F/T hrw 3-14-96
ANDA Acknowledgement Letter!

Danbury Pharmacal, Inc.
131 West Street
Danbury, CT 06810

Tel. 203 744-7200
Fax 203 798-6161

SCHEIN
PHARMACEUTICAL

February 29, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Debarment Certification

Reference: Mexiletine Hydrochloride Capsules 150 mg, 200 mg and 250 mg

Gentlemen:

In accordance with the requirement of section 306(k) of the Federal Food, Drug, and Cosmetic Act, Danbury Pharmacal, Inc. certifies that, to the best of our knowledge, Danbury Pharmacal did not use any person debarred under subsections (a) or (b) of section 306 in any capacity in connection with this ANDA, nor will Danbury Pharmacal use any such person in connection with this ANDA.

Furthermore, Danbury Pharmacal certifies that, to the best of our knowledge, the following employee of an affiliated company used by Danbury Pharmacal who, as Executive Vice President and Chief Scientific Officer, would have been among the employees overseeing work on data for the development or submission of this ANDA, has been convicted within the last five years for acts described in subsection (a) and/or (b) of section 306:

Mark B. Perkal, Ph.D.
Executive Vice President and
Chief Scientific Officer
PharmaKinetics Laboratories Inc.
302 West Fayette Street
Baltimore, MD 21201

2723

PharmaKinetics pleaded guilty on June 18, 1991 to an information containing one count alleging a violation of 18 U.S.C. section 1505 (obstruction of an investigation by the Food and Drug Administration). PharmaKinetics' conviction resulted from the conviction of a former senior employee of the company (Mark B. Perkal, Ph.D.) on a similar charge. Dr. Perkal's employment with PharmaKinetics was terminated in November, 1990 and effective November 29, 1993 Dr. Perkal was permanently debarred from providing services in any capacity to a person with an approved or pending drug product application. No information or data were generated in support of our ANDA at PharmaKinetics prior to November, 1990.

A copy of PharmaKinetics' letter of December 3, 1993 regarding Debarment Certification is attached for your information.

Sincerely,

William R. McIntyre

William R. McIntyre, Ph.D.
Director, Regulatory and Professional Affairs