CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74865

Trade Name Mexiletine Hydrochloride Capsules USP 150mg, 200mg and 250mg

Generic Name Mexiletine Hydrochloride Capsules USP 150mg, 200mg and 250mg

Sponsor Danbury Pharmacal, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74865

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74865

APPROVAL LETTER

ANDA 74-865

APR 13 1998

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

Dear Sir:

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.

Reference is also made to your amendments dated October 10, 1997; and March 4, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Mexiletine Hydrochloride Capsules USP, 150 mg, 200 mg and 250 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Mexitil® Capsules, 150 mg, 200 mg and 250 mg, respectively, of Boehringer Ingelheim). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253

(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74865

FINAL PRINTED LABELING

SCHEIN
PHARMACEUTICAL

NDC 0364-2643-02 1000 Capsules

MEXILETINE HCl
Capsules, USP

250 mg

TAKE WITH FOOD OR ANTACID

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains:
Mexiletine Hydrochloride, USP, 250 mg

Usual dosage: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

STORE BELOW 30°C (86°F).

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 3 0364-2643-02 5

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2641-01 100 Capsules

MEXILETINE HCl
Capsules, USP

150 mg

LABEL SAMPLE

TAKE WITH FOOD OR ANTACID

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains:
Mexiletine Hydrochloride, USP, 150 mg

Usual dosage: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

STORE BELOW 30°C (86°F).

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 3 0364-2641-01

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2641-05 500 Capsules

MEXILETINE HCl
Capsules, USP

150 mg

TAKE WITH FOOD OR ANTACID

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains:
Mexiletine Hydrochloride, USP, 150 mg

Usual dosage: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

STORE BELOW 30°C (86°F).

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 3 0364-2641-05 2

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2641-02 1000 Capsules

MEXILETINE HCl
Capsules, USP

150 mg

SCHEIN
PHARMACEUTICAL

NDC 0364-2643-05 500 Capsules

MEXILETINE HCl
Capsules, USP

250 mg

TAKE WITH FOOD OR ANTACID

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains:
Mexiletine Hydrochloride, USP, 250 mg

Usual dosage: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

STORE BELOW 30°C (86°F).

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 3 0364-2643-05 6

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2642-01 100 Capsules

MEXILETINE HCl
Capsules, USP

200 mg

LABEL SAMPLE

TAKE WITH FOOD OR ANTACID

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains:
Mexiletine Hydrochloride, USP, 200 mg

Usual dosage: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

STORE BELOW 30°C (86°F).

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 3 0364-2642-01 1

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2642-05 500 Capsules

MEXILETINE HCl
Capsules, USP

200 mg

TAKE WITH FOOD OR ANTACID

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains:
Mexiletine Hydrochloride, USP, 200 mg

Usual dosage: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

STORE BELOW 30°C (86°F).

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 3 0364-2642-05 9

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2642-02 1000 Capsules

MEXILETINE HCl
Capsules, USP

200 mg

TAKE WITH FOOD OR ANTACID

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains:
Mexiletine Hydrochloride, USP, 200 mg

Usual dosage: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

STORE BELOW 30°C (86°F).

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 3 0364-2642-02 8

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2643-01 100 Capsules

MEXILETINE HCl
Capsules, USP

250 mg

TAKE WITH FOOD OR ANTACID

Caution: Federal law prohibits dispensing without prescription.

Each capsule contains:
Mexiletine Hydrochloride, USP, 250 mg

Usual dosage: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

STORE BELOW 30°C (86°F).

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 8 0364-2643-01 8

Control Number and Expiration Date

MEXILETINE HYDROCHLORIDE Capsules, USP

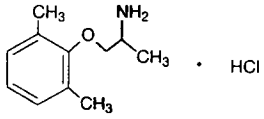
Revised: September 1996

13

DESCRIPTION

Mexiletine hydrochloride is an orally active antiarrhythmic agent available as 150 mg, 200 mg or 250 mg capsules. 100 mg of mexiletine hydrochloride is equivalent to 83.31 mg of mexiletine base. It is a white to off-white crystalline powder with a slightly bitter taste, freely soluble in water and in alcohol. Mexiletine hydrochloride has a pKa of 9.2.

Chemically, mexiletine hydrochloride is 1-methyl-2-(2,6-xylyloxy)-ethylamine hydrochloride and has the following structural formula:



$C_{11}H_{17}NO \cdot HCl$ M.W. 215.72

Each capsule, for oral administration, contains 150 mg, 200 mg or 250 mg mexiletine hydrochloride. In addition, each capsule contains the following inactive ingredients: colloidal silicon dioxide, magnesium stearate and pregelatinized starch. The capsule shells contain: black iron oxide, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide and yellow iron oxide. The 250 mg capsule shell also contains: FD&C Blue No. 1. The ink imprinted on the capsule shells contains the following ingredients: D&C Yellow No. 10 (aluminum lake), FD&C Blue No. 1 (aluminum lake), FD&C Blue No. 2 (aluminum lake), FD&C Red No. 40 (aluminum lake), pharmaceutical glaze, propylene glycol and synthetic black iron oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Mexiletine hydrochloride is a local anesthetic, antiarrhythmic agent, structurally similar to lidocaine, but orally active. In animal studies, mexiletine has been shown to be effective in the suppression of induced ventricular arrhythmias, including those induced by glycoside toxicity and coronary artery ligation. Mexiletine, like lidocaine, inhibits the inward sodium current, thus reducing the rate of rise of the action potential, Phase 0. Mexiletine decreased the effective refractory period (ERP) in Purkinje fibers. The decrease in ERP was of lesser magnitude than the decrease in action potential duration (APD), with a resulting increase in the ERP/APD ratio.

Electrophysiology in Man

Mexiletine is a Class 1B antiarrhythmic compound with electrophysiologic properties in man similar to those of lidocaine, but dissimilar from quinidine, procainamide, and disopyramide.

In patients with normal conduction systems, mexiletine has a minimal effect on cardiac impulse generation and propagation. In clinical trials, no development of second-degree or third-degree AV block was observed. Mexiletine did not prolong ventricular depolarization (QRS duration) or repolarization (QT intervals) as measured by electrocardiography. Theoretically, therefore, mexiletine may be useful in the treatment of ventricular arrhythmias associated with prolonged QT interval.

In patients with pre-existing conduction defects, depression of the sinus rate, prolongation of sinus node recovery time, decreased conduction velocity and increased effective refractory period of the intraventricular conduction system have occasionally been observed.

The antiarrhythmic effect of mexiletine has been established in controlled comparative trials against placebo, quinidine, procainamide and disopyramide. Mexiletine hy-

[illegible] may be useful in the treatment of ventricular arrhythmias associated with prolonged QT interval.

In patients with pre-existing conduction defects, depression of the sinus rate, prolongation of sinus node recovery time, decreased conduction velocity and increased effective refractory period of the intraventricular conduction system have occasionally been observed.

The antiarrhythmic effect of mexiletine has been established in controlled comparative trials against placebo, quinidine, procainamide and disopyramide. Mexiletine hydrochloride, at doses of 200 to 400 mg q8h, produced a significant reduction of ventricular premature beats, paired beats, and episodes of non-sustained ventricular tachycardia compared to placebo and was similar in effectiveness to the active agents. Among all patients entered into the studies, about 30% in each treatment group had a 70% or greater reduction in PVC count and about 40% failed to complete the three-month studies because of adverse effects. Follow-up of patients from the controlled trials has demonstrated continued effectiveness of mexiletine in long-term use.

Hemodynamics

Hemodynamic studies in a limited number of patients, with normal or abnormal myocardial function, following oral administration of mexiletine hydrochloride, have shown small, usually not statistically significant, decreases in cardiac output and increases in systemic vascular resistance, but no significant negative inotropic effect. Blood pressure and pulse rate remain essentially unchanged. Mild depression of myocardial function, similar to that produced by lidocaine, has occasionally been observed following intravenous mexiletine therapy in patients with cardiac disease.

Pharmacokinetics

Mexiletine is well absorbed (~90%) from the gastrointestinal tract. Unlike lidocaine, its first-pass metabolism is low. Peak blood levels are reached in two to three hours. In normal subjects, the plasma elimination half-life of mexiletine is approximately 10 to 12 hours. It is 50 to 60% bound to plasma protein, with a volume of distribution of 5 to 7 liters/kg. Mexiletine is metabolized in the liver. Approximately 10% is excreted unchanged by the kidney. While urinary pH does not normally have much influence on elimination, marked changes in urinary pH influence the rate of excretion: acidification accelerates excretion, while alkalinization retards it.

Several metabolites of mexiletine have shown minimal antiarrhythmic activity in animal models. The most active is the minor metabolite N-methylmexiletine, which is less than 20% as potent as mexiletine. The urinary excretion of N-methylmexiletine in man is less than 0.5%. Thus the therapeutic activity of mexiletine is due to the parent compound.

Hepatic impairment prolongs the elimination half-life of mexiletine. In eight patients with moderate to severe liver disease, the mean half-life was approximately 25 hours.

Consistent with the limited renal elimination of mexiletine, little change in the half-life has been detected in patients with reduced renal function. In eight patients with creatinine clearance less than 10 mL/min, the mean plasma elimination half-life was 15.7 hours; in seven patients with creatinine clearance between 11 to 40 mL/min, the mean half-life was 13.4 hours.

The absorption rate of mexiletine is reduced in clinical situations such as acute myocardial infarction in which gastric emptying time is increased. Narcotics, atropine and magnesium-aluminum hydroxide have also been reported to slow the absorption of mexiletine. Metoclopramide has been reported to accelerate absorption.

Mexiletine plasma levels of at least 0.5 mcg/mL are generally required for therapeutic response. An increase in the frequency of central nervous system adverse effects has been observed when plasma levels exceed 2 mcg/mL. Thus the therapeutic range is approximately 0.5 to 2 mcg/mL. Plasma levels within the therapeutic range can be attained with either three times daily or twice daily dosing but peak to trough differences are greater with the latter regimen, creating the possibility of adverse effects at peak and arrhythmic escape at trough. Nevertheless, some patients may be transferred successfully to the twice daily regimen (see **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND USAGE

Mexiletine hydrochloride capsules are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening.

therapeutic response. An increase in the frequency of central nervous system adverse effects has been observed when plasma levels exceed 2 mcg/mL. Thus the therapeutic range is approximately 0.5 to 2 mcg/mL. Plasma levels within the therapeutic range can be attained with either three times daily or twice daily dosing but peak to trough differences are greater with the latter regimen, creating the possibility of adverse effects at peak and arrhythmic escape at trough. Nevertheless, some patients may be transferred successfully to the twice daily regimen (see **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND USAGE

Mexiletine hydrochloride capsules are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Because of the proarrhythmic effects of mexiletine, its use with lesser arrhythmias is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided.

Initiation of mexiletine treatment, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital.

Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.

CONTRAINDICATIONS

Mexiletine hydrochloride capsules are contraindicated in the presence of cardiogenic shock or pre-existing second- or third-degree AV block (if no pacemaker is present).

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%). 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 experience abnormal liver function tests have been reported, some in the first few weeks of therapy with mexiletine hydrochloride. Most of these have been observed in the setting of congestive heart failure or ischemia and their relationship to mexiletine has not been established.

PRECAUTIONS

General

If a ventricular pacemaker is operative, patients with second or third degree heart block may be treated with mexiletine hydrochloride if continuously monitored. A limited number of patients (45 to 475 in controlled clinical trials) with pre-existing first degree AV block were treated with mexiletine; none of these patients developed second or third degree AV block. Caution should be exercised when it is used in such patients or in patients with pre-existing sinus node dysfunction or intraventricular conduction abnormalities.

Like other antiarrhythmics mexiletine hydrochloride can cause worsening of arrhythmias. This has been uncommon in patients with less serious arrhythmias (frequent premature beats or non-sustained ventricular tachycardia: see **ADVERSE REACTIONS**), but is of greater concern in patients with life-threatening arrhythmias such as sustained ventricular tachycardia. In patients with such arrhythmias subjected to programmed electrical stimulation or to exercise provocation, 10 to 15% of patients had exacerbation of the arrhythmia, a rate not greater than that of other agents.

Mexiletine should be used with caution in patients with hypotension and severe congestive heart failure because of the potential for aggravating these conditions.

Since mexiletine is metabolized in the liver, and hepatic impairment has been reported to prolong the elimination half-

SGOT Elevation and Liver Injury

In three-month controlled trials, elevations of SGOT greater than three times the upper limit of normal occurred in about 1% of both mexiletine-treated and control patients. Approximately 2% of patients in the mexiletine compassionate use program had elevations of SGOT greater than or equal to three times the upper limit of normal. These elevations frequently occurred in association with identifiable clinical events and therapeutic measures such as congestive heart failure, acute myocardial infarction, blood transfusions and other medications. These elevations were often asymptomatic and transient, usually not associated with elevated bilirubin levels and usually did not require discontinuation of therapy. Marked elevations of SGOT (>1000 U/L) were seen before death in four patients with end-stage cardiac disease (severe congestive heart failure, cardiogenic shock).

Rare instances of severe liver injury, including hepatic necrosis, have been reported in association with mexiletine treatment. It is recommended that patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction, be carefully evaluated. If persistent or worsening elevation of hepatic enzymes is detected, consideration should be given to discontinuing therapy.

Blood Dyscrasias

Among 10,867 patients treated with mexiletine in the compassionate use program, marked leukopenia (neutrophils less than $1000/mm^3$) or agranulocytosis were seen in 0.06%, and milder depressions of leukocytes were seen in 0.08%, and thrombocytopenia was observed in 0.16%. Many of these patients were seriously ill and receiving concomitant medications with known hematologic adverse effects. Rechallenge with mexiletine in several cases was negative. Marked leukopenia or agranulocytosis did not occur in any patient receiving mexiletine alone; five of the six cases of agranulocytosis were associated with procainamide (sustained release preparations in four) and one with vinblastine. If significant hematologic changes are observed, the patient should be carefully evaluated, and, if warranted, mexiletine should be discontinued. Blood counts usually return to normal within one month of discontinuation. (See **ADVERSE REACTIONS**.)

Convulsions (seizures) did not occur in mexiletine controlled clinical trials. In the compassionate use program, convulsions were reported in about 2 of 1000 patients. Twenty-eight percent of these patients discontinued therapy. Convulsions were reported in patients with and without a prior history of seizures. Mexiletine should be used with caution in patients with known seizure disorder.

Drug Interactions

In a large compassionate use program, mexiletine has been used concurrently with commonly employed antianginal, antihypertensive, and anticoagulant drugs without observed interactions. A variety of antiarrhythmics such as quinidine or propranolol were also added, sometimes with improved control of ventricular ectopy. When phenytoin or other hepatic enzyme inducers such as rifampin and phenobarbital have been taken concurrently with mexiletine, lowered mexiletine plasma levels have been reported. Monitoring of mexiletine plasma levels is recommended during such concurrent use to avoid ineffective therapy.

In a formal study, benzodiazepines were shown not to affect mexiletine plasma concentrations. ECG intervals (PR, QRS and QT) were not affected by concurrent mexiletine and digoxin, diuretics, or propranolol.

Concurrent administration of cimetidine and mexiletine has been reported to increase, decrease, or leave unchanged mexiletine plasma levels; therefore patients should be followed carefully during concurrent therapy.

Mexiletine does not alter serum digoxin levels, but magnesium-aluminum hydroxide, when used to treat gastrointestinal symptoms due to mexiletine, has been reported to lower serum digoxin levels.

Concurrent use of mexiletine and theophylline may lead to increased plasma theophylline levels. One controlled study in eight normal subjects showed a 72% mean increase (range 35 to 136%) in plasma theophylline levels. This increase was observed at the first test point which was the second day after starting mexiletine. Theophylline plasma levels returned to pre-mexiletine values within 48 hours after discontinuing mexiletine. If mexiletine and

theophylline are to be used concurrently, theophylline blood levels should be monitored, particularly when the mexiletine dose is changed. An appropriate adjustment in theophylline dose should be considered.

Additionally, in one controlled study in five normal subjects and seven patients, the clearance of caffeine was decreased 50% following the administration of mexiletine.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Studies of carcinogenesis in rats (24 months) and mice (18 months) did not demonstrate any tumorigenic potential. Mexiletine was found to be non-mutagenic in the Ames test. Mexiletine did not impair fertility in the rat.

Pregnancy/Teratogenic Effects

Pregnancy Category C

Reproduction studies performed with mexiletine in rats, mice and rabbits at doses up to four times the maximum human oral dose (24 mg/kg in a 50 kg patient) revealed no evidence of teratogenicity or impaired fertility but did show an increase in fetal resorption. There are no adequate and well-controlled studies in pregnant women; this drug should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Mexiletine appears in human milk in concentrations similar to those observed in plasma. Therefore, if the use of mexiletine is deemed essential, an alternative method of infant feeding should be considered.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Mexiletine hydrochloride commonly produces reversible gastrointestinal and nervous system adverse reactions but is otherwise well tolerated. Mexiletine has been evaluated in 483 patients in one-month and three-month controlled studies and in over 10,000 patients in a large compassionate use program. Dosages in the controlled studies ranged from 600 to 1200 mg/day; some patients (8%) in the compassionate use program were treated with higher daily doses (1600 to 3200 mg/day). In the three-month controlled trials comparing mexiletine to quinidine, procainamide and disopyramide, the most frequent adverse reactions were upper gastrointestinal distress (41%), lightheadedness (10.5%), tremor (12.6%) and coordination difficulties (10.2%). Similar frequency and incidence were observed in the one-month placebo-controlled trial. Although these reactions were generally not serious, and were dose-related and reversible with a reduction in dosage, by taking the drug with food or antacid or by therapy discontinuation, they led to therapy discontinuation in 40% of patients in the controlled trials. A tabulation of the adverse events reported in the one-month placebo-controlled trial follows:

COMPARATIVE INCIDENCE (%) OF ADVERSE EVENTS AMONG PATIENTS TREATED WITH MEXILETINE AND PLACEBO IN THE 4-WEEK, DOUBLE-BLIND CROSSOVER TRIAL

	Mexiletine N = 53	Placebo N = 49
Cardiovascular		
Palpitations	7.5	10.2
Chest Pain	7.5	4.1
Increased Ventricular Arrhythmias/PVCs	1.9	-
Digestive		
Nausea/Vomiting/Heartburn	39.6	6.1
Central Nervous System		
Dizziness/Lightheadedness	26.4	14.3
Tremor	13.2	-
Nervousness	11.3	6.1
Coordination Difficulties	9.4	-
Changes in Sleep Habits	7.5	16.3
Paresthesias/Numbness	3.8	2.0
Weakness	1.9	4.1
Fatigue	1.9	2.0
Tinnitus	1.9	4.1
Confusion/Clouded Sensorium	1.9	2.0
Other		
Headache	7.5	6.1
Blurred Vision/Visual Disturbances	7.5	2.0
Dyspnea/Respiratory	5.7	10.2
Rash	3.8	2.0
Non-specific Edema	3.8	-

A tabulation of adverse reactions occurring in one percent or more of patients in the three-month controlled studies follows:

COMPARATIVE INCIDENCE (%) OF TREATED WITH MEXILETINE OR CL DLE-BLIND TRIALS

	Mexiletine N = 430	C N
Cardiovascular		
Palpitations	4.3	
Chest Pain	2.6	
Angina/Angina-like Pain	1.7	
Increased Ventricular Arrhythmias/PVCs	1.0	
Digestive		
Nausea/Vomiting/Heartburn	39.3	
Diarrhea	5.2	
Constipation	4.0	
Changes in Appetite	2.6	

Rash	3.8	2.0
Non-specific Edema	3.8	-

A tabulation of adverse reactions occurring in one percent or more of patients in the three-month controlled studies follows:

COMPARATIVE INCIDENCE (%) OF ADVERSE EVENTS AMONG PATIENTS TREATED WITH MEXILETINE OR CONTROL DRUGS IN THE 12-WEEK DOUBLE-BLIND TRIALS

	Mexiletine N = 530	Quinidine N = 282	Procainamide N = 78	Disopyramide N = 69
Cardiovascular				
Palpitations	4.3	4.6	1.3	5.8
Chest Pain	2.6	3.4	1.3	2.9
Angina/Angina-like Pain	1.7	1.9	2.6	2.9
Increased Ventricular Arrhythmias/ PVCs	1.0	2.7	2.6	-
Digestive				
Nausea/Vomiting/ Heartburn	39.3	21.1	33.3	14.5
Diarrhea	5.2	33.2	2.6	8.7
Constipation	4.0	-	6.4	11.6
Changes in Appetite	2.6	1.9	-	-
Abdominal Pain/ Cramps/Discomfort	1.2			
Central Nervous System				
Dizziness/ Lightheadedness	18.9			
Tremor	13.2	14.1	1.3	2.9
Coordination Difficulties	9.7	2.3	-	1.4
Disorders in Sleep Habits	7.1	1.1	1.3	
Weakness	5.0	2.7	11.5	8.7
Nervousness	5.0	5.3	7.7	2.9
Fatigue	3.8	1.9	6.4	5.8
Speech Difficulties	2.6	5.7	5.1	1.4
Confusion/Clouded Sensorium	2.6	0.4	-	-
Paresthesias/Numbness	2.4	-	3.8	-
Tinnitus	2.4	2.3	2.6	-
		1.5	-	-
				1.4
Other				
Dizziness/ Blurred Vision/ Visual Disturbances	5.7	3.1	5.1	7.2
Headache	4.2	6.9	7.7	4.3
Rash	3.3	3.8	10.3	1.4
Dyspnea/Respiratory	3.1	3.1	5.1	2.9
Dry Mouth	2.9	1.9	5.1	14.5
Arthralgia	1.7	2.3	5.1	1.4
Fever	1.2	3.1	2.6	-
Depression				1.4

Less than 1%: Syncope, edema, hot flashes, hypertension, short-term memory loss, loss of consciousness, other psychological changes, diaphoresis, urinary hesitancy/retention, malaise, impotence/decreased libido, pharyngitis, congestive heart failure.

An additional group of over 10,000 patients has been treated in a program allowing administration of mexiletine hydrochloride under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy. Twenty-four percent of the patients continued in the program for one year or longer. Adverse reactions leading to therapy discontinuation occurred in 15 percent of patients (usually upper gastrointestinal system or nervous system effects). In general, the more common adverse reactions were similar to those in the controlled trials. Less common adverse events possibly related to mexiletine use include:

Cardiovascular System: Syncope and hypotension, each about 6 in 1000; bradycardia, about 4 in 1000; angina/angina-like pain, about 3 in 1000; edema, atrioventricular block/conduction disturbances and hot flashes, each about 2 in 1000; atrial arrhythmias, hypertension and cardiogenic shock, each about 1 in 1000.

Central Nervous System: Short-term memory loss, about 9 in 1000 patients; hallucinations and other psychological changes, each about 3 in 1000; psychosis and convulsions/seizures, each about 2 in 1000; loss of consciousness, about 6 in 10,000.

Digestive: Dysphagia, about 2 in 1000; peptic ulcer, about 8 in 10,000; upper gastrointestinal bleeding, about 7 in 10,000; esophageal ulceration, about 1 in 10,000. Rare cases of severe hepatitis/acute hepatic necrosis.

Skin: Rare cases of exfoliative dermatitis and Stevens-Johnson Syndrome with mexiletine hydrochloride treatment have been reported.

Laboratory: Abnormal liver function tests, about 5 in 1000 patients; positive ANA and thrombocytopenia, each about 2 in 1000; leukopenia (including neutropenia and agranulocytosis), about 1 in 1000; myelofibrosis, about 2 in 10,000 patients.

Other: Diaphoresis, about 6 in 1000; altered taste, about 5 in 1000; salivary changes, hair loss and impotence/de-

tions and other psychological changes, each about 3 in 1000; psychosis and convulsions/seizures, each about 2 in 1000; loss of consciousness, about 6 in 10,000.

Digestive: Dysphagia, about 2 in 1000; peptic ulcer, about 8 in 10,000; upper gastrointestinal bleeding, about 7 in 10,000; esophageal ulceration, about 1 in 10,000. Rare cases of severe hepatitis/acute hepatic necrosis.

Skin: Rare cases of exfoliative dermatitis and Stevens-Johnson Syndrome with mexiletine hydrochloride treatment have been reported.

Laboratory: Abnormal liver function tests, about 5 in 1000 patients; positive ANA and thrombocytopenia, each about 2 in 1000; leukopenia (including neutropenia and agranulocytosis), about 1 in 1000; myelofibrosis, about 2 in 10,000 patients.

Other: Diaphoresis, about 6 in 1000; altered taste, about 5 in 1000; salivary changes, hair loss and impotence/decreased libido, each about 4 in 1000; malaise, about 3 in 1000; urinary hesitancy/retention, each about 2 in 1000; hiccups, dry skin, laryngeal and pharyngeal changes and changes in oral mucous membranes, each about 1 in 1000; SLE syndrome, about 4 in 10,000.

Hematology: Blood dyscrasias were not seen in the controlled trials but did occur among the 10,867 patients treated with mexiletine in the compassionate use program (see **PRECAUTIONS**).

Myelofibrosis was reported in two patients in the compassionate use program: one was receiving long-term thiotepa therapy and the other had pretreatment myeloid abnormalities.

In postmarketing experience, there have been isolated, spontaneous reports of pulmonary changes including pulmonary fibrosis during mexiletine therapy with or without other drugs or diseases that are known to produce pulmonary toxicity. A causal relationship to mexiletine therapy has not been established. In addition, there have been isolated reports of exacerbation of congestive heart failure in patients with pre-existing compromised ventricular function. There have been rare reports of pancreatitis associated with mexiletine treatment.

OVERDOSAGE

Clinical findings associated with mexiletine overdosage have included nausea, hypotension, sinus bradycardia, paresthesia, seizures, bundle branch block, AV heart block, asystole, ventricular tachyarrhythmia, 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.

DOSAGE AND ADMINISTRATION

The dosage of mexiletine hydrochloride must be individualized on the basis of response and tolerance, both of which are dose-related. Administration with food or antacid is recommended. Initiate mexiletine hydrochloride therapy with 200 mg every eight hours when rapid control of arrhythmia is not essential. A minimum of two to three days between dose adjustments is recommended. Dose may be adjusted in 50 or 100 mg increments up or down.

As with any antiarrhythmic drug, clinical and electrocardiographic evaluation (including Holter monitoring if necessary for evaluation) are needed to determine whether the desired antiarrhythmic effect has been obtained and to guide titration and dose adjustment.

Satisfactory control can be achieved in most patients by 200 to 300 mg given every eight hours with food or antacid. If satisfactory response has not been achieved at 300 mg q8h, and the patient tolerates mexiletine well, a dose of 400 mg q8h may be tried. As the severity of CNS side effects increases with total daily dose, the dose should not exceed 1200 mg/day.

In general, patients with renal failure will require the usual doses of mexiletine hydrochloride. Patients with severe liver disease, however, may require lower doses and must be monitored closely. Similarly, marked right-sided congestive heart failure can reduce hepatic metabolism and reduce the needed dose. Plasma level may also be affected by certain concomitant drugs (see **PRECAUTIONS: Drug Interactions**).

can reduce hepatic metabolism and reduce the needed dose. Plasma level may also be affected by certain concomitant drugs (see **PRECAUTIONS: Drug Interactions**).

Loading Dose

When rapid control of ventricular arrhythmia is essential, an initial loading dose of 400 mg of mexiletine may be administered, followed by a 200 mg dose in eight hours. Onset of therapeutic effect is usually observed within 30 minutes to two hours.

Q12H Dosage Schedule

Some patients responding to mexiletine may be transferred to a 12-hour dosage schedule to improve convenience and compliance. If adequate suppression is achieved on a mexiletine dose of 300 mg or less every eight hours, the same total daily dose may be given in divided doses every 12 hours while carefully monitoring the degree of suppression of ventricular ectopy. This dose may be adjusted up to a maximum of 450 mg every 12 hours to achieve the desired response.

Transferring to Mexiletine hydrochloride

The following dosage schedule, based on theoretical considerations rather than experimental data, is suggested for transferring patients from other Class I oral antiarrhythmic agents to mexiletine hydrochloride: mexiletine hydrochloride treatment may be initiated with a 200 mg dose, and titrated to response as described above, 6 to 12 hours after the last dose of quinidine sulfate, 3 to 6 hours after the last dose of procainamide, 6 to 12 hours after the last dose of disopyramide or 8 to 12 hours after the last dose of tocainide.

In patients in whom withdrawal of the previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, hospitalization of the patient is recommended.

When transferring from lidocaine to mexiletine hydrochloride, the lidocaine infusion should be stopped when the first oral dose of mexiletine is administered. The infusion line should be left open until suppression of the arrhythmia appears to be satisfactorily maintained. Consideration should be given to the similarity of the adverse effects of lidocaine and mexiletine and the possibility that they may be additive.

HOW SUPPLIED

Mexiletine Hydrochloride Capsules, USP 150 mg are #2, light brown opaque and brown opaque capsules imprinted "MEXILETINE HCl 150" and "DAN 5870" supplied in bottles of 100, 500 and 1000.

Mexiletine Hydrochloride Capsules, USP 200 mg are #1, light brown opaque capsules imprinted "MEXILETINE HCl 200" and "DAN 5871" supplied in bottles of 100, 500 and 1000.

Mexiletine Hydrochloride Capsules, USP 250 mg are #0 light brown opaque and aqua blue opaque capsules imprinted "MEXILETINE HCl 250" and "DAN 5872" supplied in bottles of 100, 500 and 1000.

Dispense in a tight, light-resistant container with a child-resistant closure.

Store below 30°C (86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

Revised: September 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74865

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.2

2. ANDA #74-865

3. NAME AND ADDRESS OF APPLICANT
Danbury Pharmacal, Inc.
Attention: William R. McIntyre, Ph.D.
131 West Street
Danbury, CT 06810

4. LEGAL BASIS FOR SUBMISSION
Mexitil Capsules; Boehringer Ingelheim. Patent expired on May 04, 1995 and no expiration date for exclusivity.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Mexiletine Hydrohloride Capsules, USP

7. NONPROPRIETARY NAME
Mexiletine Hydrohloride Capsules, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firms:
February 29, 1996: Original submission
October 10, 1997: Major amendment

FDA:
March 18, 1996: Acknowledgement letter
August 26, 1996: Deficiency letter

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA-N18873

13. DOSAGE FORM
Oral Capsule

14. POTENCY
150 mg, 200 mg and 250 mg

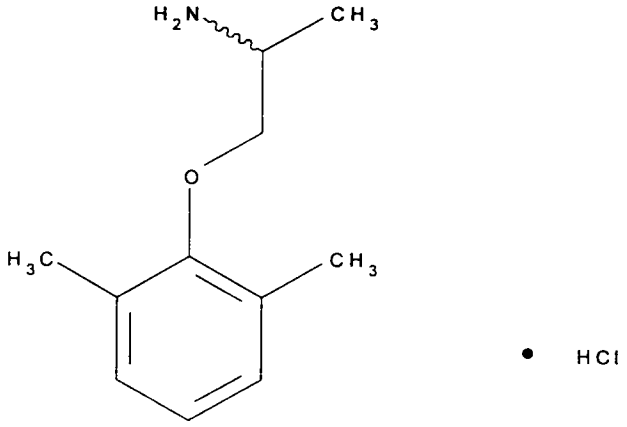
15. CHEMICAL NAME AND STRUCTURE

2-propanamine, 1-(2,6-dimethylphenoxy)-, hydrochloride, (±).

(±)-1-methyl-2-(2,6-xylyloxy)ethylamine hydrochloride.
[CAS# 5370-01-04]

Mexiletine Hydrochloride USP

$C_{11}H_{17}NO.HCl$; M.W. = 215.72



1-Methyl-2-(2,6-xylyloxy)ethylamine hydrochloride.
CAS [5370-01-04]

16. RECORDS AND REPORTS

Debarment commitment from Danbury and
are provided on page 2723 and 2725 in section XXI.
authorization letter is provided on page 2733 in section XXI.
authorization letter is provided on page 2734 in section XXI.

17. COMMENTS

The following deficiencies are found:
- EER pending

18. CONCLUSIONS AND RECOMMENDATIONS

The application can be approved. A approvable letter is pending acceptable EER.

19. REVIEWER: Sema Basaran, Ph.D.

DATE COMPLETED: 2-2-98