PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]MINT-MEXILETINE

Mexiletine Hydrochloride

Capsules, 100 mg and 200 mg, Oral

USP

Antiarrhythmic Agent

Mint Pharmaceuticals Inc.
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Mississauga, Ontario, L5T 2M3

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RECENT MAJOR LABEL CHANGES

None.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MINT–MEXILETINE (mexiletine hydrochloride) is indicated for:

- the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia.
- the treatment of patients with documented symptomatic ventricular arrhythmias when the symptoms are of sufficient severity to require treatment. Because of the proarrhythmic effects of mexiletine, its use should be reserved for patients in whom, in the opinion of the physician, the benefit of treatment clearly outweighs the risks.

1.1 Pediatrics

The safety and efficacy of mexiletine in children has not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

No data are available.

2 CONTRAINDICATIONS

- MINT–MEXILETINE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Hypersensitive to local anesthetics of amide type (e.g.,lidocaine)
- Second or third degree Atrioventricular block (AV block) in the absence of a pacemaker
- Cardiogenic shock.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

- **Mortality**

  No antiarrhythmic drug has been shown to reduce the incidence of sudden death in patients with asymptomatic ventricular arrhythmias. Most antiarrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increased incidence of sudden death. In light of the above, physicians should carefully consider the risk and benefits of antiarrhythmic therapy for all patients with ventricular arrhythmias.

- **Acute Liver Injury**

  Abnormalities of the liver function and rare instances of severe liver injury, including hepatic necrosis have been reported in association with mexiletine treatment. (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- A small proportion of patients and those with severe liver disease may require lower doses since these doses have been shown to produce effective plasma levels in some patients.
- When transferring from lidocaine to mexiletine, the lidocaine infusion should be stopped when the first oral dose of mexiletine is administered. The infusion line should be kept in place in case the arrhythmia reappears and requires additional lidocaine to suppress it. Consideration should be given to the similarity of the adverse effects of lidocaine and mexiletine and the possibility that they may be additive.

4.2 Recommended Dose and Dosage Adjustment

The optimal dosage should be determined individually based on the patient's response and tolerance.

The suggested initial dose is 200 mg 3 times daily. This can be raised to a maximum 1200 mg daily, given in 3 or 4 divided doses. Titration of dose should occur in steps of 100 mg 3 times daily. At least 3 days are needed between each dosage change. The dose usually producing therapeutic response is between 600–900 mg daily. A small proportion of patients and those with severe liver disease may require lower doses such as 100 mg 3–4 times daily, since these doses have been shown to produce effective plasma levels in some patients

In patients in whom rapid control of ventricular arrhythmia is needed, a loading dose of 400 mg may be given. This should be followed by 200 mg administered 3 times daily, beginning 8 hours after the administration of the loading dose.

Information on the appropriate regimen for the transfer from intravenous lidocaine to mexiletine is lacking.

4.4 Administration

- Mexiletine should be taken with ample liquid, food and/or an antacid.
- For patients with sustained ventricular tachycardia, mexiletine therapy should be initiated in the hospital. Hospitalization may also be required for certain other patients depending on their cardiac status and underlying cardiac disease.

4.5 Missed Dose

If patient misses a dose, it should be taken immediately unless the time is close to the next dose. In such an event, patient should wait for next scheduled dose and continue on the regular schedule. A double dose should not be taken to make up for a missed dose.

5 OVERDOSAGE

Symptoms of overdosage of mexiletine were nausea, hypotension, bradycardia, paresthesia, left bundle branch block, asystole convulsions and death. Treatment should be supportive and may include gastric lavage and atropine for cardiovascular complications.

Animal studies have indicated that benzodiazepines have a protective effect against mexiletine induced convulsions. Acidification of the urine enhances mexiletine elimination.

There have been 11 reports of overdose; 3 were fatal. One fatality involved a healthy 22 year old male who ingested about 4.4 g of mexiletine. His symptoms were paresthesias, nausea and generalized convulsions. On admission to the hospital, his pulse rate was 15 beats/min., blood pressure was not recordable and the ECG showed complete heart block with a slow escape rhythm followed by ventricular asystole. This patient did not respond to any treatment. The blood level of mexiletine was 34 to 37 µg/mL at the time of death.

Another fatality involved a male who started convulsing at home after taking an unknown quantity of mexiletine. The convulsions were uncontrolled by diazepam, phenytoin and phenobarbital and the patient died following aspiration and ventricular fibrillation. A post mortem at 26 hours found cardiac blood levels of mexiletine of 25 µg/mL.

Details of the third fatality are not available.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Oral	Capsule/100 mg, 200 mg	Colloidal Silicon Dioxide, Magnesium Stearate, Pregelatinized Starch *Capsule shell:* **100 mg:** FD&C blue 1, FD&C Red 3, FD&C Red 40, FD&C Yellow 6, Gelatin, Purified water, Sodium Lauryl Sulphate, Titanium Dioxide. TekPrint SW-0012 White Ink: Shellac, Dehydrated Alcohol, Isopropyl Alcohol, Butyl Alcohol, Propylene Glycol, Strong Ammonia Solution, Potassium Hydroxide, Titanium Dioxide **200 mg:** FD&C Yellow 6, Gelatin, Purified Water, Titanium Dioxide TekPrint SW-9008 Black Ink: Shellac, Dehydrated Alcohol, Isopropyl Alcohol, Butyl Alcohol, Propylene Glycol, Strong Ammonia Solution, Black Iron Oxide, Potassium Hydroxide,

Description

100 mg - White granular powder in a hard gelatin capsule with a Scarlet opaque cap and an Orange opaque body, imprinted with "A36" on the cap and “100" on the body in white ink. Available in bottles of 100.

200 mg - White granular powder in a hard gelatin capsule with an Orange opaque cap and an Orange opaque body, imprinted with "A28" on the cap and "200" on the body in black ink. Available in bottles of 100.

7 WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

Animal studies demonstrated that mexiletine is not carcinogenic. Ames test did not show any mutagenic activity by mexiletine. See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity.

Cardiovascular

Atrioventricular (AV) Block: If a ventricular pacemaker is operative, patients with second or third degree AV block may be treated with MINT–MEXILETINE if continuously monitored. Caution should be exercised when MINT– MEXILETINE is used in patients with first degree AV block.

Congestive Heart Failure or Hypotension: MINT–MEXILETINE (mexiletine hydrochloride) should be used cautiously in patients with hypotension or congestive heart failure because of its potential for depressing myocardial contractility.

The results of the Cardiac Arrhythmia Suppression Trial (CAST) in post-myocardial infarction patients with asymptomatic ventricular arrhythmias showed a significant increase in mortality and in non-fatal cardiac arrest rate in patients treated with encainide or flecainide compared with a matched placebo- treated group. CAST was continued using a revised protocol with the moricizine and placebo arms only. The trial was prematurely terminated because of a trend towards an increase in mortality in the moricizine treated group.

The applicability of these results to other populations or other antiarrhythmic agents in uncertain, but at present it is prudent to consider these results when using an antiarrhythmic agent.

Intraventricular Conduction Abnormalities: Caution should be exercised when MINT-MEXILETINE is used.

Proarrhythmic Effects: Mexiletine has been reported to aggravate or induce arrhythmias in some patients. In the 398 patients studied in North American controlled clinical trials in whom evaluation was possible, mexiletine induced or aggravated pre-existing arrhythmias in 3.8%. The incidence as reported in the literature has ranged from 8 to 29%.

In the subgroup of patients with life-threatening arrhythmias subjected to programmed electrical stimulation or to exercise, 10 to 15% of the patients had exacerbation of their arrhythmias.

Sinus Node Dysfunction: Caution should be exercised when MINT– MEXILETINE is used in patients with pre–existing sinus node dysfunction (e.g., sick sinus syndrome).

Driving and Operating Machinery

Because mexiletine can cause central nervous system effects such as light-headedness/dizziness, tremor and coordination difficulty, patients should be warned about engaging in activities requiring mental alertness, judgement and physical coordination (such as driving an automobile or operating machinery) when these effects occur.

Genitourinary

Urinary pH: Since renal excretion of mexiletine is greatly increased with acidification of urine, concomitant drug therapy or dietary regimens which substantially change urinary pH should be avoided while being treated with MINT–MEXILETINE.

Hematologic

Blood Dyscrasias: Blood dyscrasias were not seen in the controlled trials, but in the compassionate use program, leukopenia, neutropenia, agranulocytosis and thrombocytopenia have been reported in a small number of patients. Although causal relationship has not been clearly established, such a relationship cannot be excluded. Therefore, it is recommended that careful hematologic monitoring should be carried out in patients on mexiletine. Hemogram including WBC differential and platelet count should be performed prior to initiation of therapy. If significant hematologic changes are observed, the patients should be carefully evaluated, and, if warranted, mexiletine should be discontinued. Blood counts usually returned to normal within one month of discontinuation (see 8 ADVERSE REACTIONS).

Hypokalemia: Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected as part of the management of ventricular arrhythmia.

Hepatic/Biliary/Pancreatic

Hepatic

Patients with Liver Disease:
Since mexiletine is metabolized in the liver, and hepatic impairment has been reported to prolong the elimination half–life of mexiletine, patients with liver disease should be followed carefully while receiving MINT–MEXILETINE. The same caution should be observed in patients with hepatic dysfunction secondary to congestive heart failure.

Liver Injury: Abnormalities of the liver function and 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, considerations should be given to discontinuing therapy.

Monitoring and Laboratory Tests

Having an amphetamine-like chemical structure, mexiletine interferes with the assay used in some rapid urine drug screens, which can result in false positive readings, particularly for amphetamines. A positive result should usually be confirmed with a more specific method.

Neurologic

Seizures: MINT–MEXILETINE should be used with caution in patients with known seizure disorders. In the compassionate use programme, seizures were reported in approximately 0.2% of the patients with or without a prior history of seizures. Therapy was discontinued in 28% of those patients.

7.1 Special Populations

7.1.1 Pregnant Women

The safe use of mexiletine during pregnancy has not been determined. The expected benefits of using MINT–MEXILETINE when pregnancy is present or suspected must be weighed against possible risks to the fetus. Studies in animals showed no embryotoxic nor teratogenic effects.

7.1.2 Breast-feeding

Mexiletine is found in human milk in concentrations that are comparable to those observed in plasma. Thus, if mexiletine therapy is considered necessary, an alternative method of infant feeding should be considered.

7.1.3 Pediatrics

The safety and efficacy of mexiletine in children has not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

No data is available.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions to mexiletine were upper gastrointestinal distress (22%), lightheadedness (8.6%) and tremor (8%). These were usually mild and were reversible with a reduction in dose or withdrawal of the drug. The most severe adverse effect was the induction or aggravation of pre–existing arrhythmia (see 7 WARNINGS AND PRECAUTIONS). About 16% of patients had mexiletine discontinued because of side effects. Upper gastrointestinal distress was the adverse effect most commonly responsible for discontinuation of mexiletine.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse experiences (incidence≥ 1%) were observed among 10 321 patients given mexiletine in controlled and open clinical trials. The majority of patients were seriously ill and undergoing multiple drug therapy.

Table 2 - Adverse Events (incidence≥ 1%)

	Incidence Rate	Adverse Event
Cardiovascular (See 7 WARNINGS AND PRECAUTIONS)	1 1 1	Arrhythmia Palpitations CHF
Central Nervous System (See 7 WARNINGS AND PRECAUTIONS)	8.6 8 3.1 2.5 2.3 2.2 1.8 1.7 1.5 1.2	Light-headedness Tremor Coordination difficulties Changes in sleep habits Weakness Fatigue Nervousness Clouded sensorium Paresthesias Depression
Gastrointestinal	22 2.3 2 1.7 1.2 1	Upper gastrointestinal distress Changes in appetite Constipation Abdominal pain/ cramps/discomfort Diarrhea Dry mouth
Respiratory	1	Dyspnea
Other	2.1 1.7 1.4	Vision problems Rash Headache

8.5 Post Market Adverse Reactions

Adverse effects occurring in less than 1% of patients are indicated below in decreasing order of incidence.

Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS): Drug reactions with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking Mexiletine. DRESS typically presents with eosinophilia, fever, rash, and/or lymphadenopathy in association

with other organ involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Discontinue Mexiletine if DRESS is suspected.

Hepatic disorders:

Acute Liver Injury: In post-marketing 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 hydrochloride has not been established.

In foreign marketing experience, rare instances of severe liver injury, including hepatic necrosis, have been reported in association with mexiletine treatment.(See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS).

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).

Cardiovascular: 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.

Dermatological: (0.1% to 1%) diaphoresis, loss of hair, dry skin. Rare cases of exfoliative dermatitis and Stevens-Johnson Syndrome have been reported in association with mexiletine treatment.

Digestive: (0.1% to 1%) abdominal gas/bloating, dysphagia, hiccups, altered taste, salivary changes. (< 0.1%) upper GI inflammation, upper GI bleeding, peptic ulcer, esophageal ulceration. There have been rare reports of severe hepatitis/acute hepatic necrosis.

Genitourinary: (0.1% to 1%) impotence/decreased libido, urinary hesitancy/retention. (< 0.1%) renal failure.

Hematological: thrombocytopenia (0.16%), neutropenia (0.16%), agranulocytosis (0.16%), leukopenia (0.11%). Agranulocytosis occurred in 8 patients (including 2 patients with myelofibrosis) in the emergency use program. It occurred mostly after 1 to 6 weeks of therapy. All patients were also taking procainamide and/or other agents known to be associated with hematological disorders. Four patients died. Systemic Lupus Erythematosus was also reported in the emergency use program at a ratio of 4/10 000.

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.

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. There have been rare reports of pancreatitis associated with Mexiletine treatment.

Laboratory: Abnormal liver function tests, about 5 in 1000; 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.

Respiratory:
In post-marketing experience, there have been isolated, spontaneous reports of pulmonary changes including pulmonary fibrosis in association with other drugs or diseases known to produce pulmonary toxicity. A causal relationship to mexiletine therapy has not been established.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview.

Since mexiletine hydrochloride 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. With involvement of CYP2D6, there can be either poor or extensive metabolizer phenotypes.

9.4 Drug-Drug Interactions

CYP2D6 and CYP1A2: Since mexiletine hydrochloride 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, QT, 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.

Tocainide/Lidocaine: Concomitant use of mexiletine and lidocaine or tocainide may lead to potentiation of adverse effects involving the CNS.

Other Cardiovascular Agents: Mexiletine has been used clinically in combination with cardiac glycosides, other antiarrhythmic agents (quinidine, procainamide, and disopyramide), diuretics and anticoagulants without evidence of serious untoward effects. In some cases addition of another antiarrhythmic achieved improved control of ventricular ectopy. It is however possible that concurrent use may produce additive effects and dosage adjustments may be necessary.

Mexiletine has no effect on digoxin serum levels.

Hepatic Enzyme Inducers: Drugs which induce hepatic enzymes such as phenytoin, rifampicin and phenobarbital increase the non–renal clearance of mexiletine. Thus, a higher dose of MINT-MEXILETINE may be needed when these agents are started while the patient is on mexiletine therapy. Likewise, discontinuation of therapy with these drugs may require a lowering of MINT-MEXILETINE dose.

Cimetidine: Cimetidine has been reported to have a variety of effects on mexiletine absorption and plasma levels. During concomitant treatment, the patient should be carefully monitored for the emergence of adverse effects.

Theophylline: There have been rare reports of increased serum levels of theophylline after concurrent therapy with mexiletine. Adverse effects typical of elevated serum levels of theophylline (i.e., nausea, vomiting, tremor) have occurred. Therefore, patients should be observed during concurrent therapy with the two drugs and serum theophylline concentrations should be monitored. A decrease in theophylline dosage may be required.

Metoclopramide: Metoclopramide through its action on gastric motility, produces faster absorption and higher peak blood levels of mexiletine. No change in the maintenance dosage is required as bioavailability is not altered.

Agents Which Alter Gastrointestinal Activity: Narcotic analgesics, anticholinergics magnesium hydroxide and aluminum hydroxide delay the absorption of mexiletine. The bioavailability and clearance of mexiletine are not altered and therefore no change in the maintenance dosage of mexiletine is recommended in patients receiving these drugs.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

MINT-MEXILETINE (mexiletine hydrochloride) is a class 1B antiarrhythmic agent, according to the Vaughan–Williams classification system, with local anesthetic properties, similar in structure and activity to lidocaine.

10.2 Pharmacodynamics

Mexiletine blocks the fast sodium channel in cardiac tissues, especially the Purkinje network, without involvement of the autonomic system. Mexiletine reduces the rate of rise and amplitude of the action potential and decreases automatically (increases the threshold of excitability) in the Purkinje fibers. It shortens the action potential duration and, to a lesser extent, decreases the effective refractory period in the Purkinje fibers. It does not usually alter conduction velocity, although it may slow conduction in patients with pre- existing conduction abnormalities. In those with pre-existing sick sinus syndrome, mexiletine produces a more pronounced depression of the sinus rate and/or prolongation of sinus node recovery time. It does not significantly affect resting membrane potential or sinus node automaticity, left ventricular function, systolic arterial blood pressure, atrioventricular (AV) conduction velocity, QRS or QT intervals.

Hemodynamic studies with oral mexiletine conducted in patients with normal or abnormal myocardial function have demonstrated that the drug usually has only minor effects on cardiac output, pulmonary capillary wedge pressure, left ventricular end–diastolic pressure, pulmonary diastolic pressure, blood pressure or heart rate.

Small increases in vascular resistance without significant negative inotropic effects have also been observed.

In Vitro:

Electrophysiological experiments in isolated tissues have shown that mexiletine, in therapeutic concentrations, produces a lengthening of sino–atrial conduction time (5×10^{-6}M) and an increase in the atrial action potential duration (10^{-7}M) with no effect on the spontaneous cycle length. Mexiletine produces a reduction in the rate of rise of the action potential (10^{-6}M) and of the action potential duration in Purkinje fibres (5×10^{-6}M). Studies have also demonstrated that conduction across the Purkinje fibre–ventricular muscle junction is significantly lengthened by mexiletine, but only at toxic concentrations (10^{-4}M).

The mexiletine concentration required to reduce the frequency of the spontaneous beating rate of the isolated guinea pig atrium by 30% was approximately 37 mg/L and by 50%, 52 mg/L. In isolated rabbit atria, contraction amplitude decreased by 31% and 42% 2 hours following exposure to 3 and 5 µg/mL, respectively.

Mexiletine produced local anesthetic effects in the rabbit cornea model at a concentration of 0.5%.

In Vivo:
Intravenous doses of 2 and 4 mg/kg were injected in dogs. There were no alterations in intra–atrial or intra–ventricular conduction in spontaneously beating or paced hearts (120 beats/min.). A–V conduction time was prolonged by 17% by the 4mg/kg dose in spontaneously beating hearts and by 32% in paced hearts. Heart rate was reduced by 12% and 13%, respectively, at both doses.

Experiments in anesthetized dogs demonstrated that contractility (dp/dt max.) was decreased by 17% after 2 mg/kg and by 32% following 4 mg/kg mexiletine i.v.

In anesthetized cats and dogs, intravenous doses up to 1 mg/kg did not affect arterial pressure or flow volume. The left ventricular and diastolic pressure rose by 1.1 and 1.6 mm Hg at doses of 2 and 4 mg/kg, respectively, and the right ventricular systolic pressure was reduced by 4 and 2 mm Hg at these respective doses. Systolic and diastolic aortic pressures did not change at 2 mg/kg but decreased by 17% and 20%, respectively at 4 mg/kg. All other measured parameters remained unaltered.

Interactions between mexiletine and several other drugs were observed in mice. Superadditive effects on the LD_{50} were observed between i.v. mexiletine and lidocaine, oral mexiletine and oral verapamil, oral and i.v. mexiletine and oral and i.v. quinidine, i.v. mexiletine and i.v. propranolol, oral mexiletine and oral procainamide, i.v. mexiletine and i.v. procaine.

Protection against mexiletine–induced convulsions and death in chicks was provided by chlordiazepoxide, oxazepam, diazepam and phenobarbital.

The cardiovascular interaction of mexiletine and propranolol was observed in anesthetized dogs. Dogs were administered 0.3 mg/kg propranolol, 2 mg/kg mexiletine, 0.6 mg/kg propranolol and 4 mg/kg mexiletine sequentially, with the appropriate time interval between

each i.v. dose. The following statistically significant changes were seen following mexiletine in addition to those produced by propranolol: reduction in heart rate by 8% (low dose), reduced left ventricular systolic pressure by 8% and 21% at low and high doses, raised left ventricular end–diastolic pressure by 29% and 313% at low and high doses, reduced maximal rate of increase in pressure (dp/dt max.) by 22% and 41% at low and high doses, reduced right ventricular systolic pressure by 8% at the low dose, reduced aortic systolic pressure by 6% and 19% at low and high doses, reduced aortic diastolic pressure by 22% at the high dose, decreased aortic flow by 19% and 30% at low and high doses, reduced femoral flow by 24% and 23% at low and high doses, longer isometric contraction time by 12% at the low dose and prolonged atrioventricular conduction time (PQ) by 4% at the low dose.

Mexiletine was shown to possess anticonvulsant activity in mice after maximum electroshock, having an oral ED50 of 19 to 28 mg/kg. Mexiletine 10 mg/kg i.p. also protected against convulsions produced by electrical and chemical stimulation of the amygdala.

Mexiletine does not antagonize alpha or beta adrenergic receptors and is not a calcium antagonist.

10.3 Pharmacokinetics

Absorption

Mexiletine is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are attained within 2 to 4 hours after oral administration. The systemic bioavailability of mexiletine is about 90%. The apparent volume of distribution is large (5 to 10 L/kg) reflecting the extensive uptake of the drug by tissues. Protein binding has been estimated to be about 55 to 70%.

The optimal plasma range is approximately 0.5 to 2 μg/mL. The therapeutic efficacy as well as the frequency of side effects proportionately increases as the blood level rises. There is little therapeutic response with plasma concentrations less than 0.5 μg/mL and a significant rise in adverse reactions, particularly those in CNS, have been observed when plasma concentrations are greater than 2 μg/mL.

Elimination

Mexiletine is mainly eliminated by hepatic metabolism with approximately 10% being excreted unchanged in the urine. In humans, the major metabolites are 4– hydroxy–mexiletine, hydroxymethyl mexiletine, and their corresponding alcohols which are devoid of antiarrhythmic activity. The most active metabolite is N-methylmexiletine which is 20% as potent as mexiletine. The urinary excretion of this metabolite in man is less than 0.5%.

Mexiletine does not undergo any significant first pass elimination. In patients with ventricular arrhythmias, the elimination half–life ($t_{1/2}$) is about 12.1 ± 4 hours (mean ± SD) as compared to 9.7 ± 1.9 hours in normal volunteers. Urinary acidosis increases the renal clearance of mexiletine.

Delayed and incomplete absorption as well as prolonged elimination ($t_{1/2}$ about 24 hours) has been associated with an acute myocardial infarction.

Special Populations and Conditions

- **Hepatic / Renal Insufficiency**

Prolongation of the $t_{1/2}$ was also seen in patients with liver dysfunction ($t_{1/2}$ approximately 25 hours), impaired renal function (creatinine clearance 10 mL/min: $t_{1/2}$ = 15.7 hours, creatinine clearance 11 to 40 mL/min: $t_{1/2}$ = 13.4 hours) and in patients free of hepatic or renal involvement but with severe left ventricular failure ($t_{1/2}$ = about 15.4 hours ± 5.8 hours) (See 9 DRUG INTERACTIONS).

11 STORAGE, STABILITY AND DISPOSAL

Bottles should be stored between 15°–30°C.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

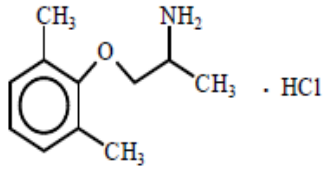
Drug Substance

Proper name: Mexiletine Hydrochloride

Chemical name: 2-Propanamine, 1-(2,6-dimethylphenoxy)-, hydrochloride, (±)-
(±)-1-Methyl-2-(2,6-xylyloxy)ethylamine hydrochloride

Molecular formula and molecular mass: $C_{11}H_{17}NO \cdot HCl$ 215.72 g/mol

Structural formula:



Physiochemical properties: Mexiletine hydrochloride is a white to almost white, almost odourless, crystalline powder. It is freely soluble in water, methanol and ethanol, sparingly soluble in chloroform and practically insoluble in ether. The melting point range is 202.30°–203.47°C.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

MINT-MEXILETINE (mexiletine hydrochloride) 100 mg and 200 mg capsules have satisfied the criteria for a Biopharmaceutics Classification System (BCS)-based biowaiver in comparison to the respective strengths of ^{Pr}TEVA-MEXILETINE (mexiletine hydrochloride) capsules (Teva Canada Limited).

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

Table 3 – Acute Toxicity:

Species	Route of Administration	LD50 (mg/kg)
Mouse	p.o. s.c. i.m. i.p. i.v.	260–400 170–255 128–135 125–140 35–50_
Rat	p.o. s.c. i.m. i.p. i.v.	330–630 500–720 190–260 76–79_ 27–30_
Dog	p.o. s.c. i.v.	112–356 65–85_ 18–60_

The symptoms of toxicity were ataxia, excitement, mydriasis and convulsions.

Subacute and Chronic Toxicity: A 13 week oral study in rats using doses of 15, 30, 60 and 150 mg/kg (increased to 175 mg/kg at week 7 and 200 mg/kg at week 9) was conducted. A decrease in body weight gain and a fatty degeneration of the liver cells was observed in the 2 highest dose groups.

Two 26 week experiments were carried out in rats using doses of 20, 40, 80 and 120 mg/kg. Convulsions occurred in animals receiving 80 mg/kg and most rats receiving the highest dose.

Mortality was greater in the 120 mg/kg group. There were increases in the adrenal weights in males and in the ovaries and thyroid of females.

Dogs were administered 3, 9 and 15 mg/kg (increased to 20 mg/kg on day 29 and 30_mg/kg on day 57) orally for 13 weeks. Vomiting occurred more frequently in the treated animals. Fatty changes of myocardial fibres were observed in the 2 highest dose groups and a peripheral fatty change in the liver was observed in one animal receiving the highest dose.

Two additional studies of 27 and 52 weeks duration were carried out using doses of 5, 10, 20 and 40 mg/kg. A transient increase in heart rate was noted and 3 out of 6 high dose animals died (after 36 weeks) in the 52 week study. Ataxia, tremors, excess salivation and convulsions occurred at 40_mg/kg. Fatty changes of the liver cells were observed in one animal receiving 20 mg/kg and 4 dogs in the 40 mg/kg group in one study.

Dogs were administered 1.5, 3, and 13.5 mg/kg i.v. for 4 weeks. Muscular incoordination, ataxia and convulsions were produced by the high dose. Heart rate was also transiently increased.

A 4 week experiment was performed in monkeys given 1.5, 4.5 and 12 mg/kg i.v. Ataxia, muscle incoordination and convulsions were observed in the high dose group.

An 18 month experiment was carried out in rats given 20, 40 and 240_mg/kg mexiletine orally. There was a decrease in appetite and in body weight gain in the high dose group. Elevations in SGPT and AP were also observed in this group. Histological evaluation did not show any drug–induced changes.

Oral doses of 5, 10, 20 and 40 mg/kg were given to dogs for a period of one year. There was frequent vomiting in the animals of the 2 high dose groups. In the group receiving the highest dose, excessive salivation, ataxia, tremors, convulsions and a transient increase in heart rate were observed and 3 animals in this group died. Fatty changes were observed in the livers of 1/6 controls, 2/6 low and 2/6 mid–dose dogs.

Mutagenicity: Ames tests in *Salmonella typhimurium* using up to 3000 μg/plate did not result in any sign of mutagenic activity by mexiletine.

Carcinogenicity: Eighteen month carcinogenicity experiments in mice and 2 year experiments in rats were conducted using oral doses of up to 160 mg/kg and 240 mg/kg, respectively. These studies showed that mexiletine does not possess tumorigenic or carcinogenic effects.

Reproductive and Developmental Toxicology: Fertility studies were performed in female rats given oral doses of 20, 40 and 60 mg/kg 2 weeks before mating and continuing throughout gestation. The results showed that mexiletine had no effect on spermatogenesis, oogenesis or fertility. A similar peri– and postnatal experiment using oral doses of up to 60 mg/kg/day given during gestation and lactation had no effect on development or behavior during rearing, or reproduction in the F1 generation.

Experiments were carried out in mice given 40 and 80 mg/kg, rats given 50 and 100 mg/kg and rabbits given 40 and 80 mg/kg to determine if mexiletine possesses teratogenic effects. Mexiletine was given from the 6th to 18th day of gestation. Although the highest doses produced toxic effects in pregnant females (usually convulsions), there was no sign of embryotoxic or teratogenic effects caused by mexiletine.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Mexitil® Capsules, 100 mg and 200 mg, Product Monograph, Boehringer Ingelheim (Canada) Ltd., March 9, 1989.
2. PrTEVA-MEXILETINE Capsules, 100 mg and 200 mg, Product Monograph, Teva Canada Limited, November 27, 2023.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]MINT-MEXILETINE

mexiletine hydrochloride capsules

Read this carefully before you start taking **MINT-MEXILETINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MINT-MEXILETINE**.

Serious Warnings and Precautions

- MINT-MEXILETINE is intended for use only in patients with life-threatening irregular heartbeats (arrhythmias). Most anti-arrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increase of sudden death. Your healthcare professional will tell you about the risk and benefits of anti-arrhythmic therapy.

- MINT-MEXILETINE can cause liver problems including rare instances of death of liver cells. Your healthcare professional will monitor your health and may adjust your dose of MINT-MEXILETINE**.**

What is MINT-MEXILETINE used for?

MINT-MEXILETINE is used in adults to treat certain types of irregular heartbeat conditions known as ventricular arrhythmias.

How does MINT-MEXILETINE work?

MINT-MEXILETINE is an antiarrhythmic agent. It works by blocking certain electrical signals in the heart that can cause an irregular heartbeat.

What are the ingredients in MINT-MEXILETINE?

Medicinal ingredient: mexiletine hydrochloride

Non-medicinal Ingredients: Colloidal Silicon Dioxide, Magnesium Stearate, Pregelatinized Starch

The capsule shell is made of:

100mg: FD&C blue 1, FD&C Red 3, FD&C Red 40, FD&C Yellow 6, Gelatin, Purified water, Sodium Lauryl Sulphate, Titanium Dioxide.

TekPrint SW-9008 Black Ink:
Shellac, Dehydrated Alcohol, Isopropyl Alcohol, Butyl Alcohol, Propylene Glycol, Strong Ammonia Solution, Black Iron Oxide, Potassium Hydroxide,

200 mg**:** FD&C Yellow 6, Gelatin, Purified Water, Titanium Dioxide

TekPrint SW- White Ink:
Shellac, Dehydrated Alcohol, Isopropyl Alcohol, Butyl Alcohol, Propylene Glycol, Strong Ammonia Solution, Potassium Hydroxide, Titanium Dioxide.

MINT-MEXILETINE comes in the following dosage forms:

Capsules: 100 mg and 200 mg

Do not use MINT-MEXILETINE if:

- you are allergic to mexiletine hydrochloride or to any of the ingredients in MINT-MEXILETINE.
- you are or have experienced allergic reactions to local anesthetics that are amide type such as lidocaine
- you have second or third degree atrioventricular block (a type heart rhythm disorder that causes the heart to beat slowly or skip beats) and do not have a pacemaker
- you have a heart condition called cardiogenic shock (heart is not able to pump enough blood to the body)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MINT-MEXILETINE. Talk about any health conditions or problems you may have, including if you:

- have low blood pressure (hypotension)
- have heart problems including:
  - heart failure
  - atrioventricular block
  - heart conduction problems
  - sinus node dysfunction, a heart rhythm disorder
- have low levels of potassium in your blood
- have liver problems
- have a seizure disorder
- are taking medicine or foods that change the acidity of your urine. Talk to your healthcare professional if you are not sure.
- are pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed. MINT-MEXILETINE passes into breast milk. Talk to your healthcare professional about the best way to feed your baby during this time.

Other warnings you should know about:

Monitoring and Tests: Before you start treatment and during your treatment with MINT-MEXILETINE, your healthcare professional may perform tests to monitor your:

- heart. MINT-MEXILETINE and other antiarrhythmic drugs can cause new heart rhythm problems or worsen existing ones.
- liver.
- blood, bone marrow and lymph nodes.

Your healthcare professional will interpret your results and may adjust your dose or stop your treatment with MINT-MEXILETINE.

Driving and using machines: MINT-MEXILETINE can cause light headedness, dizziness, tremors and difficulty with coordination. Before you drive or do tasks that require special attention, wait until you know how MINT-MEXILETINE affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MINT-MEXILETINE:

- medicines known to affect the activity of CYP2D6 and CYP1A2 enzymes such as propafenone and fluvoxamine
- lidocaine, used to numb an area of the body and reduce pain
- other antiarrhythmic agents such as tocainide, quinidine, procainamide, and disopyramide
- medicines known as cardiac glycosides, used to treat heart failure and irregular heartbeats
- medicines known as diuretics (“water pills”), used to lower blood pressure
- medicines known as anticoagulants, used to prevent blood clotting
- medicines that increase the activity of liver enzymes, such as phenytoin, rifampin, and phenobarbital
- cimetidine, used to treat heartburn and stomach ulcers
- theophylline, used to treat asthma, bronchitis and other breathing problems
- metoclopramide, used to prevent nausea and vomiting
- narcotic analgesics, used to provide relief from pain
- magnesium hydroxide and aluminum hydroxide, used to relieve heartburn, acid indigestion and upset stomach
- anticholinergics medicines, used to treat incontinence, overactive bladder, respiratory disorders or Parkinson disease

How to take MINT-MEXILETINE:

- Take MINT-MEXILETINE exactly as your healthcare professional tells you. Do not increase or decrease your dose without talking to your healthcare professional.
- MINT-MEXILETINE should be taken with liquid, food and/or an antacid.

Usual dose:
Your healthcare professional will determine the right dose of MINT-MEXILETINE for you. The usual initial dose is 200 mg three times a day. Your healthcare professional may decide on a different dose depending on:

- your response and tolerance to MINT-MEXILETINE
- if you have liver problems
- if you have heart problems

Overdose:

Some of the signs of an overdose include:

- nausea
- low blood pressure
- slow heart rhythm
- sensation of tingling, pain or numbness in hands, fingers and toes
- heart conduction problems

If you think you, or a person you are caring for, have taken too much MINT-MEXILETINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss taking your dose, take it as soon as you remember. But if it is almost time for you to take the next dose, skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using MINT-MEXILETINE?

These are not all the possible side effects you may have when taking MINT-MEXILETINE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- feeling lightheaded, weak, fatigued or nervous
- tremor
- difficulty with coordination
- changes in sleep habits
- having trouble thinking clearly or concentrating
- sensation of tingling, pain or numbness in hands, fingers and toes
- changes in appetite
- constipation

- stomach pain, cramps, or discomfort
- diarrhea
- dry mouth
- shortness of breath
- vision problems
- rash
- headache
- excessive sweating
- loss of hair
- dry skin
- changes in libido
- changes in taste

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Upper gastrointestinal problems: heartburn, nausea, vomiting, stomach pain, or difficulty swallowing	√		
COMMON			
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat		√	
Congestive Heart Failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Depression (sad mood that won't go away)**:** difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse		√	
Palpitation (fast-beating, fluttering or pounding heart): skipping beats, beating too fast, pounding, fluttering rapidly		√	
UNCOMMON			
Angina: (not enough oxygen to the heart muscle): discomfort in the shoulder, arm, back, throat, jaw or teeth; pain or pressure in the chest		√	
Bradycardia (abnormally slow heartbeat)		√	
Cardiogenic shock (heart is not able unable to pump enough blood to the organs of the body): breathe fast, fast heartbeat, loss of consciousness, sweating, pale skin, cold hands or feet			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Edema: unusual swelling of the arms, hands, legs, feet and ankles, face or airway passages		√	
Hallucinations: seeing or hearing things that are not there		√	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		√	
Seizures (fits)**:** uncontrollable shaking with or without loss of consciousness			√
Syncope (fainting)**:** a temporary loss of consciousness due to a sudden drop in blood pressure		√	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		√	
Neutropenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms		√	
RARE			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hepatic necrosis (death of liver cells): abdominal pain and dark urine, fever, light-colored stool, and jaundice (a yellow appearance of the skin and white portion of the eyes)			√
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			√
Stevens-Johnson syndrome (SJS) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			√
UNKNOWN FREQUENCY			
Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect one or more organs): fever, severe rash, peeling skin, swelling of the face, swollen lymph glands, flu- like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feel thirsty, urinating less often, less urine			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Kidney failure (severe kidney problems): confusion; itchiness or rashes; puffiness in your face and hands; swelling in your feet or ankles; urinating less or not at all; weight gain.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html)) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15° - 30°C.

Keep out of reach and sight of children.

If you want more information about MINT-MEXILETINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.mintpharmaceuticals.com), or by calling 1-877-398-9696.

This leaflet was prepared by Mint Pharmaceuticals Inc.
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