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Cardiología

1. Fludrocortisone

2. Midodrine

3. Sotalol

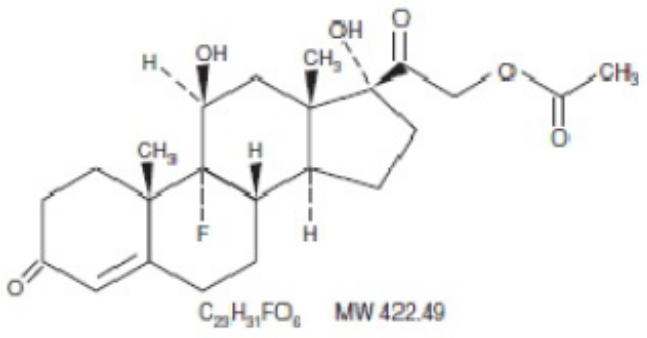
4. Mexiletine

FLUDROCORTISONE ACETATE- fludrocortisone acetate tablet
West-ward Pharmaceutical Corp

Fludrocortisone Acetate Tablets, USP

Description

Fludrocortisone Acetate Tablets contain fludrocortisone acetate, a synthetic adrenocortical steroid possessing very potent mineralocorticoid properties and high glucocorticoid activity; it is used only for its mineralocorticoid effects. The chemical name for fludrocortisone acetate is 9-fluoro-11ß,17,21-trihydroxypregn-4-ene-3,20-dione 21-acetate; its structural formula is:



Fludrocortisone Acetate Tablets are available for oral administration as scored tablets providing 0.1 mg fludrocortisone acetate per tablet. Inactive ingredients: anhydrous lactose, corn starch, lactose monohydrate, magnesium stearate, sugar, and talc.

Clinical Pharmacology

Corticosteroids are thought to act, at least in part, by controlling the rate of synthesis of proteins. Although there are a number of instances in which the synthesis of specific proteins is known to be induced by corticosteroids, the links between the initial actions of the hormones and the final metabolic effects have not been completely elucidated.

The physiologic action of fludrocortisone acetate is similar to that of hydrocortisone. However, the effects of fludrocortisone acetate, particularly on electrolyte balance, but also on carbohydrate metabolism, are considerably heightened and prolonged. Mineralocorticoids act on the distal tubules of the kidney to enhance the reabsorption of sodium ions from the tubular fluid into the plasma; they increase the urinary excretion of both potassium and hydrogen ions. The consequence of these three primary effects together with similar actions on cation transport in other tissues appear to account for the entire spectrum of physiological activities that are characteristic of mineralocorticoids. In small oral doses, fludrocortisone acetate produces marked sodium retention and increased urinary potassium excretion. It also causes a rise in blood pressure, apparently because of these effects on electrolyte levels.

In larger doses, fludrocortisone acetate inhibits endogenous adrenal cortical secretion, thymic activity, and pituitary corticotropin excretion; promotes the deposition of liver glycogen; and, unless protein intake is adequate, induces negative nitrogen balance.

The approximate plasma half-life of fludrocortisone (fluorohydrocortisone) is 3.5 hours or more and the biological half-life is 18 to 36 hours.

Indications and Usage

Fludrocortisone Acetate Tablets, 0.1 mg are indicated as partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease and for the treatment of salt-losing adrenogenital syndrome.

Contraindications

Corticosteroids are contraindicated in patients with systemic fungal infections and in those with a history of possible or known hypersensitivity to these agents.

Warnings

BECAUSE OF ITS MARKED EFFECT ON SODIUM RETENTION, THE USE OF FLUDROCORTISONE ACETATE IN THE TREATMENT OF CONDITIONS OTHER THAN THOSE INDICATED HEREIN IS NOT ADVISED.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. If an infection occurs during fludrocortisone acetate therapy, it should be promptly controlled by suitable antimicrobial therapy.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. However, since fludrocortisone acetate is a potent mineralocorticoid, both the dosage and salt intake should be carefully monitored in order to avoid the development of hypertension, edema, or weight gain. **Periodic checking of serum electrolyte levels is advisable during prolonged therapy; dietary salt restriction and potassium supplementation may be necessary.** All corticosteroids increase calcium excretion.

Patients should not be vaccinated against smallpox while on corticosteroid therapy. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

The use of Fludrocortisone Acetate Tablets in patients with active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary since reactivation of the disease may occur. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

Precautions

General

Adverse reactions to corticosteroids may be produced by too rapid withdrawal or by continued use of

large doses.

To avoid drug-induced adrenal insufficiency, supportive dosage may be required in times of stress (such as trauma, surgery, or severe illness) both during treatment with fludrocortisone acetate and for a year afterwards.

There is an enhanced corticosteroid effect in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition being treated. A gradual reduction in dosage should be made when possible.

Psychic derangements may appear when corticosteroids are used. These may range from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Existing emotional instability or psychotic tendencies may also be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinemia.

Corticosteroids should be used with caution in patients with nonspecific ulcerative colitis if there is a probability of impending perforation, abscess, or other pyogenic infection. Corticosteroids should also be used cautiously in patients with diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Information for Patients

The physician should advise the patient to report any medical history of heart disease, high blood pressure, or kidney or liver disease and to report current use of any medicines to determine if these medicines might interact adversely with fludrocortisone acetate (see **Drug Interactions**).

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to obtain medical advice.

The patient’s understanding of his steroid-dependent status and increased dosage requirement under widely variable conditions of stress is vital. Advise the patient to carry medical identification indicating his dependence on steroid medication and, if necessary, instruct him to carry an adequate supply of medication for use in emergencies.

Stress to the patient the importance of regular follow-up visits to check his progress and the need to promptly notify the physician of dizziness, severe or continuing headaches, swelling of feet or lower legs, or unusual weight gain.

Advise the patient to use the medicine only as directed, to take a missed dose as soon as possible, unless it is almost time for the next dose, and not to double the next dose.

Inform the patient to keep this medication and all drugs out of the reach of children.

Laboratory Tests

Patients should be monitored regularly for blood pressure determinations and serum electrolyte determinations (see **WARNINGS**).

Drug Interactions

When administered concurrently, the following drugs may interact with adrenal corticosteroids.

Amphotericin B or potassium-depleting diuretics (benzothiadiazines and related drugs, ethacrynic acid and furosemide)—enhanced hypokalemia. Check serum potassium levels at frequent intervals; use potassium supplements if necessary (see **WARNINGS**).

Digitalis glycosides—enhanced possibility of arrhythmias or digitalis toxicity associated with

hypokalemia. Monitor serum potassium levels; use potassium supplements if necessary.

Oral anticoagulants—decreased prothrombin time response. Monitor prothrombin levels and adjust anticoagulant dosage accordingly.

Antidiabetic drugs (oral agents and insulin)—diminished antidiabetic effect. Monitor for symptoms of hyperglycemia; adjust dosage of antidiabetic drug upward if necessary.

Aspirin—increased ulcerogenic effect; decreased pharmacologic effect of aspirin. Rarely salicylate toxicity may occur in patients who discontinue steroids after concurrent high-dose aspirin therapy. Monitor salicylate levels or the therapeutic effect for which aspirin is given; adjust salicylate dosage accordingly if effect is altered (see **PRECAUTIONS**, **General**).

Barbiturates, phenytoin, or rifampin—increased metabolic clearance of fludrocortisone acetate because of the induction of hepatic enzymes. Observe the patient for possible diminished effect of steroid and increase the steroid dosage accordingly.

Anabolic steroids (particularly C-17 alkylated androgens such as oxymetholone, methandrostenolone, norethandrolone, and similar compounds)—enhanced tendency toward edema. Use caution when giving these drugs together, especially in patients with hepatic or cardiac disease.

Vaccines—neurological complications and lack of antibody response (see **WARNINGS**).

Estrogen—increased levels of corticosteroid-binding globulin, thereby increasing the bound (inactive) fraction; this effect is at least balanced by decreased metabolism of corticosteroids. When estrogen therapy is initiated, a reduction in corticosteroid dosage may be required, and increased amounts may be required when estrogen is terminated.

Drug/Laboratory Test Interactions

Corticosteroids may affect the nitrobluetetrazolium test for bacterial infection and produce false-negative results.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate studies have not been performed in animals to determine whether fludrocortisone acetate has carcinogenic or mutagenic activity or whether it affects fertility in males or females.

Pregnancy

Teratogenic Effects: Category C

Adequate animal reproduction studies have not been conducted with fludrocortisone acetate. However, many corticosteroids have been shown to be teratogenic in laboratory animals at low doses. Teratogenicity of these agents in man has not been demonstrated. It is not known whether fludrocortisone acetate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fludrocortisone acetate should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects

Infants born of mothers who have received substantial doses of fludrocortisone acetate during pregnancy should be carefully observed for signs of hypoadrenalism.

Maternal treatment with corticosteroids should be carefully documented in the infant’s medical records to assist in follow up.

Nursing Mothers

Corticosteroids are found in the breast milk of lactating women receiving systemic therapy with these agents. Caution should be exercised when fludrocortisone acetate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Adverse Reactions

Most adverse reactions are caused by the drug's mineralocorticoid activity (retention of sodium and water) and include hypertension, edema, cardiac enlargement, congestive heart failure, potassium loss, and hypokalemic alkalosis.

When fludrocortisone is used in the small dosages recommended, the glucocorticoid side effects often seen with cortisone and its derivatives are not usually a problem; however the following untoward effects should be kept in mind, particularly when fludrocortisone is used over a prolonged period of time or in conjunction with cortisone or a similar glucocorticoid.

Musculoskeletal—muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, and spontaneous fractures.

Gastrointestinal—peptic ulcer with possible perforation and hemorrhage, pancreatitis, abdominal distention, and ulcerative esophagitis.

Dermatologic—impaired wound healing, thin fragile skin, bruising, petechiae and ecchymoses, facial erythema, increased sweating, subcutaneous fat atrophy, purpura, striae, hyperpigmentation of the skin and nails, hirsutism, acneiform eruptions, and hives; reactions to skin tests may be suppressed.

Neurological—convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache, and severe mental disturbances.

Endocrine—menstrual irregularities; development of the cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress (e.g., trauma, surgery, or illness); decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; and increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic—posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and exophthalmos.

Metabolic—hyperglycemia, glycosuria, and negative nitrogen balance due to protein catabolism.

Allergic Reactions—allergic skin rash, maculopapular rash, and urticaria.

Other adverse reactions that may occur following the administration of a corticosteroid are necrotizing angiitis, thrombophlebitis, aggravation or masking of infections, insomnia, syncopal episodes, and anaphylactoid reactions.

Overdosage

Development of hypertension, edema, hypokalemia, excessive increase in weight, and increase in heart size are signs of overdosage of fludrocortisone acetate. When these are noted, administration of the drug should be discontinued, after which the symptoms will usually subside within several days; subsequent treatment with fludrocortisone acetate should be with a reduced dose. Muscular weakness may develop due to excessive potassium loss and can be treated by administering a potassium supplement. Regular monitoring of blood pressure and serum electrolytes can help to prevent overdosage (see **WARNINGS**).

Dosage and Administration

Dosage depends on the severity of the disease and the response of the patient. Patients should be continually monitored for signs that indicate dosage adjustment is necessary, such as remissions or exacerbations of the disease and stress (surgery, infection, trauma) (see **WARNINGS** and **PRECAUTIONS**, **General**).

Addison's Disease

In Addison's disease, the combination of Fludrocortisone Acetate Tablets with a glucocorticoid such as hydrocortisone or cortisone provides substitution therapy approximating normal adrenal activity with minimal risks of unwanted effects.

The usual dose is 0.1 mg of Fludrocortisone Acetate Tablets daily, although dosage ranging from 0.1 mg three times a week to 0.2 mg daily has been employed. In the event transient hypertension develops as a consequence of therapy, the dose should be reduced to 0.05 mg daily. Fludrocortisone Acetate Tablets are preferably administered in conjunction with cortisone (10 mg to 37.5 mg daily in divided doses) or hydrocortisone (10 mg to 30 mg daily in divided doses).

Salt-Losing Adrenogenital Syndrome

The recommended dosage for treating the salt-losing adrenogenital syndrome is 0.1 mg to 0.2 mg of Fludrocortisone Acetate Tablets daily.

How Supplied

Fludrocortisone Acetate Tablets, USP 0.1 mg are Round, White Tablets, Scored, Debossed "W" on the plain side and "46" on scored side.

Bottles of 30 tablets
Bottles of 100 tablets

Storage

Store at 20-25ºC (68-77ºF) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, NJ 07724

Issued January 2010

Principal Display Panel

Fludrocortisone Acetate Tablets, USP
0.1 mg/30 Tablets
NDC 0143-1246-30

FLUDROCORTISONE ACETATE

fludrocortisone acetate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-1246
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FLUDROCORTISONE ACETATE (UNII: V47IF0PVH4) (FLUDROCORTISONE - UNII:U0476M545B)	FLUDROCORTISONE ACETATE	0.1 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
CORN STARCH 3-E-DODECENYL SUCCINIC ANHYDRIDE MODIFIED (UNII: QG4MW19XYX)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	W;46
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0143-1246-01	100 in 1 BOTTLE		
2	NDC:0143-1246-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091302	07/22/2011	

Labeler - West-ward Pharmaceutical Corp (001230762)

Establishment

Name	Address	ID/FEI	Business Operations
West-ward Pharmaceutical Corp		001230762	MANUFACTURE

Revised: 7/2011 West-ward Pharmaceutical Corp

PRODUCT MONOGRAPH

PrAPO-SOTALOL

Sotalol Tablets BP

as Sotalol Hydrochloride

80 mg and 160 mg

ANTIARRHYTHMIC

APOTEX INC.
150 Signet Drive
Weston, Ontario
M9L 1T9

DATE OF REVISION:
July 22, 2022

Submission Control # 265824

PRODUCT MONOGRAPH

[Pr]APO-SOTALOL

Sotalol Tablets BP

80 mg and 160 mg

THERAPEUTIC CLASSIFICATION

Antiarrhythmic

ACTIONS AND CLINICAL PHARMACOLOGY

Sotalol hydrochloride has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Sotalol hydrochloride is a racemic mixture of d- and l-sotalol. Both isomers have similar Class III antiarrhythmic effects, while the l-isomer is responsible for virtually all of the beta- blocking activity. APO-SOTALOL is non-cardio selective and is not associated with partial agonist or membrane stabilizing activity. Whereas significant beta-blockade may occur at oral doses as low as 25 mg, Class III effects are seen at daily doses of 160 mg and above. The antiarrhythmic activity of APO-SOTALOL appears to be primarily due to the drug's Class III property, based on animal models.

Pharmacologically, in addition to its antiarrhythmic properties, sotalol hydrochloride also has antihypertensive and antianginal properties.

Electrophysiology

Sotalol hydrochloride prolongs the plateau phase of the cardiac action potential in the isolated myocyte, as well as in isolated tissue preparations of ventricular and atrial muscle (Class III activity). In intact animals it slows heart rate, decreases A-V nodal conduction and increases the refractory periods of atrial and ventricular muscle and conduction tissue.
In man, the Class II (beta-blockade) electrophysiological effects of APO-SOTALOL are manifested by increased sinus cycle length, decreased AV nodal conduction and increased AV nodal refractoriness. The Class III electrophysiological effects in man include prolongation of the atrial and ventricular monophasic action potentials, and effective refractory period prolongation of atrial muscle, ventricular muscle, and atrioventricular accessory pathways (where present) in both the anterograde and retrograde directions. With oral doses of 160 to 640 mg/day, the surface ECG shows dose-related mean increases of 40-100 msec in QT and 10-40 msec in QT_c. No significant alteration in QRS interval is observed.

In a small study (n=25) of patients with implanted defibrillators treated concurrently with sotalol hydrochloride, the average defibrillatory threshold was 6 joules (range 2-15 joules) compared to a mean of 16 joules for a non-randomized comparative group primarily receiving amiodarone.

In a randomized clinical trial [Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) Trial] comparing choice of antiarrhythmic therapy by PES suppression versus Holter monitor selection (in each case followed by treadmill exercise testing) in patients with a history of sustained VT/VF who were also inducible by PES, the effectiveness acutely and chronically of sotalol hydrochloride was compared with 6 other drugs (procainamide, quinidine, mexiletine, propafenone, imipramine and pirmenol). Overall response, limited to first randomized drug, was 39% for APO-SOTALOL and 30% for the pooled other drugs. Acute response rate for first drug randomized using suppression of PES induction was 36% for sotalol hydrochloride versus a mean of 13% for the other drugs. Using the Holter monitoring endpoint (complete suppression of sustained VT, 90% suppression of NSVT, 80% suppression of VPC pairs, and at least 70% suppression of VPC's), sotalol hydrochloride yielded 41% response versus 45% for the other drugs combined. Among responders placed on long-term therapy identified acutely as effective (by either PES or Holter), sotalol hydrochloride, when compared to the pool of other drugs, had the lowest two-year mortality (13% versus 22%), the lowest two-year VT recurrence rate (30% versus 60%), and the lowest withdrawal rate (38% versus about 75-80%). The most commonly used doses of sotalol hydrochloride in this trial were 320 - 480 mg/day (66% of patients), with 16% receiving 240 mg/day or less and 18% receiving 640 mg or more.

It cannot be determined, however, in the absence of a controlled comparison of sotalol hydrochloride versus no pharmacologic treatment (e.g., in patients with implanted defibrillators) whether APO-SOTALOL response causes improved survival or identifies a population with a good prognosis.

Hemodynamics

In a study of systemic hemodynamic function measured invasively in 12 patients with a mean left ventricular (LV) ejection fraction of 37% and ventricular tachycardia (9 sustained and 3 non-sustained), a median dose of 160 mg twice daily of sotalol hydrochloride produced a 28% reduction in heart rate and a 24% decrease in cardiac index at 2 hours post-dosing at steady-state. Concurrently, systemic vascular resistance and stroke volume showed non-significant increases of 25% and 8%, respectively. Pulmonary capillary wedge pressure increased significantly from 6.4 mmHg to 11.8 mmHg in the 11 patients who completed the study. One patient was discontinued because of worsening congestive heart failure. Mean arterial pressure, mean pulmonary artery pressure and stroke work index did not significantly change. Exercise and isoproterenol induced tachycardia are antagonized by sotalol hydrochloride and total peripheral resistance increases by a small amount.

In hypertensive patients, sotalol hydrochloride produces significant reductions in both systolic and diastolic blood pressures. Although APO-SOTALOL is usually well tolerated hemodynamically, caution should be exercised in patients with marginal cardiac compensation as deterioration in cardiac performance may occur (see WARNINGS: Congestive Heart Failure).

Pharmacokinetics

In Healthy Subjects: The oral bioavailability of sotalol hydrochloride is 90 - 100%. After oral administration, peak plasma concentrations are reached in 2.5 to 4 hours, and steady-state

plasma concentrations are attained within 2-3 days. Over the dosage range of 160-640 mg/day, sotalol hydrochloride displays dose proportionality with respect to plasma concentrations. Distribution occurs to a central (plasma) and to a peripheral compartment, with a mean elimination half-life of 7 - 15 hours.

Sotalol hydrochloride does not bind to plasma proteins and is not metabolized. The pharmacokinetics of the d and l enantiomers of APO-SOTALOL are essentially identical. APO-SOTALOL crosses the blood brain barrier poorly. In one study, mean cerebrospinal fluid concentrations following a single oral dose ranged from 5% to 28% of those observed in plasma.

In Renally-Impaired Patients: Excretion is predominantly via the kidney in the unchanged form, and therefore lower doses are necessary in renal impairment (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

In Hepatically-Impaired Patients: Since sotalol hydrochloride is not subject to first-pass metabolism, patients with hepatic impairment show no alteration in clearance of sotalol hydrochloride.

In Elderly Patients: Age per se does not significantly alter the pharmacokinetics of sotalol hydrochloride, but impaired renal function in elderly patients can increase the terminal elimination half-life, resulting in increased drug accumulation.

Effect of Food: When sotalol hydrochloride was administered with a standard meal, the absorption was reduced by approximately 20% compared to that in the fasting state.
A blinded, randomized, cross-over, single-dose bioavailability study was conducted in 18 healthy male volunteers to compare the bioavailability of APO-SOTALOL (160 mg) tablets to Sotacor® (160 mg) tablets. The pharmacokinetic results are listed in the table that follows.

Summary Table of the Sotalol HCl 160 mg Tablet
Comparative Bioavailability Data
(Dose: 160 mg) (From measured data)

Geometric Mean*
Arithmetic Mean (CV%)**

Parameter	**APO-Sotalol**	**Sotacor®**	**Ratio of Means**
AUC_T	16237	16523	98.3
(ng•hr/mL)	16729 (22)	16786 (19)	
AUC_I	16703	16989	98.3
(ng•hr/mL)	17186 (22)	17241 (18)	
C_{max}	1414	1420	99.5
(ng/mL)	1459 (24)	1450 (21)	
T_{max} (hr)	3.0 (0.74)	3.4 (0.61)	
$t_{1/2}$ (hr)	10.8 (1.59)	10.7 (1.67)	

*The geometric means are presented for AUC_T, AUC_I and C_{max} parameters
**For T_{max} and $t_{1/2}$ parameters, the arithmetic means (SD) are presented

These results demonstrate the bioequivalence of these two formulations.

INDICATIONS AND CLINICAL USE

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 risks and benefits of antiarrhythmic therapy for all patients with ventricular arrhythmias.

APO-SOTALOL (sotalol hydrochloride) is indicated for the treatment of documented life-threatening ventricular arrhythmias such as sustained ventricular tachycardia. APO-SOTALOL may also be used for 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 APO-SOTALOL, its use should be reserved for patients in whom, in the opinion of the physician, the benefit of treatment clearly outweighs the risks.

For patients with sustained ventricular tachycardia, APO-SOTALOL 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.

In view of the proarrhythmic effects of APO-SOTALOL, its use in patients with hypertension or angina pectoris is not recommended unless they also require APO-SOTALOL for the treatment of ventricular arrhythmias.

CONTRAINDICATIONS

APO-SOTALOL (sotalol hydrochloride) is contraindicated in patients with bronchial asthma, allergic rhinitis, severe sinus node dysfunction, sinus bradycardia, second and third degree AV block (unless a functioning pacemaker is present), congenital or acquired long QT syndrome, cardiogenic shock, severe or uncontrolled congestive heart failure, hypokalemia, anesthesia with agents that produce myocardial depression and previous evidence of hypersensitivity to APO-SOTALOL.

WARNINGS

Mortality: 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 is uncertain, but at present it is prudent to consider these results when using any antiarrhythmic agent.

Proarrhythmia: APO-SOTALOL (sotalol hydrochloride) may cause new or worsen existing arrhythmias. Such proarrhythmic effects range from an increase in frequency of premature

ventricular contractions to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes. It is therefore essential that each patient administered APO-SOTALOL be evaluated clinically and electrocardiographically prior to, and during therapy to determine whether the response to APO-SOTALOL supports continued treatment. Sotalol hydrochloride, like some antiarrhythmic agents, has been associated with a specific form of arrhythmia, torsade de pointes, which is defined as a polymorphic ventricular tachycardia with prolongation of the QT interval and QRS complexes of changing amplitude that appear to twist around the isoelectric axis. Torsades have been observed more frequently in patients with an elevated baseline QT (>430 msec), on-therapy QT of >500 msec, bradycardia (heart rate <50 bpm), hypokalemia and hypomagnesemia (see WARNINGS, Electrolyte Disturbances) and congestive heart failure. Because of the variable temporal recurrence of arrhythmias, it is not always possible to distinguish between a new or aggravated arrhythmic event and lack of efficacy. Thus, the incidence of drug-related events cannot be precisely determined and the rates of occurrence provided below must be considered approximations. It should be noted that drug-induced arrhythmias may often not be identified until late after starting the drug because of infrequent monitoring. Due to the possibility of proarrhythmic effects, APO-SOTALOL is not recommended for the treatment of patients with asymptomatic premature contractions (see INDICATIONS AND CLINICAL USE).

Overall in clinical trials with APO-SOTALOL, 4.3% of 3257 patients experienced a new or worsened ventricular arrhythmia. Of this 4.3%, new or worsened sustained ventricular tachycardia was reported in approximately 1% of patients, and torsade de pointes in 2.4%. Additionally, in approximately 1% of patients, deaths were considered possibly drug-related; such cases, although difficult to evaluate, may have been associated with proarrhythmic events. In patients with a history of sustained ventricular tachycardia, the incidence of torsade de pointes was 4%, and worsened VT was approximately 1%; in patients with other, less serious, ventricular arrhythmias and supraventricular arrhythmias, the incidence of torsade de pointes was 1% and 1.4%, respectively.

As shown in the table below, torsade de pointes arrhythmias as well as the prolongation of QT (QT_c) interval were dose related.

Percent Incidence of Torsade de Pointes and Mean QT_c Interval by Dose for Patients with Sustained VT/VF		
Daily Dose (mg)	Incidence of Torsade de Pointes	Mean QT_c* (msec)
80	0 (69)	463 (17)
160	0.5 (832)	467 (181)
320	1.6 (835)	473 (344)
480	4.4 (459)	483 (234)
640	3.7 (324)	490 (185)
>640	5.8 (103)	512 (62)
( ) Number of patients assessed; * Highest on-therapy value		

In addition to dose and presence of sustained VT, other risk factors for torsade de pointes were gender (females had a higher incidence), excessive prolongation of the QT_c interval (see table

below) and history of cardiomegaly or congestive heart failure. Patients with sustained ventricular tachycardia and a history of congestive heart failure appear to have the highest risk for serious proarrhythmia (7%). Of the patients experiencing torsade de pointes, approximately two-thirds spontaneously reverted to their baseline rhythm. The others were either converted electrically (D/C cardioversion or overdrive pacing) or treated with other drugs (see SYMPTOMS AND TREATMENT OF OVERDOSAGE). It is not possible to determine whether some sudden deaths represented episodes of torsade de pointes, but in some instances sudden death did follow a documented episode of torsade de pointes. Although APO-SOTALOL therapy was discontinued in most patients experiencing torsade de pointes, 17% were continued on a lower dose. Nonetheless, APO-SOTALOL should be used with particular caution if the QT_c is greater than 500 msec on- therapy and serious consideration should be given to reducing the dose or discontinuing therapy when the QT_c exceeds 550 msec. Due to the multiple risk-factors associated with torsade de pointes, however, caution should be exercised regardless of the QT_c interval. The table below relates the incidence of torsade de pointes to on-therapy QT_c and change in QT_c from baseline. It should be noted, however, that the highest on-therapy QT_c was in many cases the one obtained at the time of the torsade de pointes event, so that the table overstates the predictive value of a high QT_c.

Relationship Between QT_C Interval Prolongation and Torsade de Pointes

On-Therapy QTC Interval (msec)	Incidence of Torsade de Pointes
<500	1.3% (1787)
500 – 525	3.4% (236)
525 – 550	5.6% (125)
>550	10.8% (157)

Change in QTC Interval from Baseline (msec)	Incidence of Torsade de Pointes
<65	1.6% (1516)
65 - 80	3.2% (158)
80 - 100	4.1% (146)
100 - 130	5.2% (115)
>130	7.1% (99)

( ) Number of patients assessed.

Proarrhythmic events must be anticipated not only on initiating therapy, but with every upward dose adjustment. Proarrhythmic events most often occur within 7 days of initiating therapy or of an increase in dose; 75% of serious proarrhythmias (torsade de pointes and worsened VT) occurred within 7 days of initiating APO-SOTALOL therapy, while 60% of such events occurred within 3 days of initiation or a dosage change. Initiating therapy at 80 mg b.i.d. with gradual upward dose titration and appropriate evaluations for efficacy (e.g., PES or Holter) and safety (e.g., QT interval, heart rate and electrolytes) prior to dose escalation should reduce the risk of proarrhythmia. Avoiding excessive accumulation of APO-Sotalol in patients with diminished renal function, by appropriate dose reduction, should also reduce the risk of proarrhythmia (see DOSAGE AND ADMINISTRATION).

Electrolyte Disturbances: APO -SOTALOL should not be used in patients with hypokalemia or hypomagnesemia prior to correction of such imbalance, as these conditions can exaggerate the degree of QT prolongation and increase the potential for torsade de pointes. The serum

electrolytes must be monitored regularly and more frequently if diuretics are used concomitantly. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or patients receiving concomitant diuretics.

Congestive Heart Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure (CHF), and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Moreover, patients with CHF have a higher risk of torsade de pointes (see WARNINGS, Proarrhythmia).

In patients with controlled CHF, APO-SOTALOL should be administered cautiously. The positive inotropic action of digitalis may be reduced when the two drugs are used concomitantly. Both digitalis and sotalol slow AV conduction. If cardiac failure continues despite adequate digitalization, APO-SOTALOL should be discontinued.

In patients without a history of heart failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. At the first sign of impending heart failure, appropriate therapy must be established and consideration should be given to discontinuation of treatment with APO-SOTALOL.

In clinical trials, new or worsened congestive heart failure (CHF) occurred in 3.3% (n=3257) of patients and led to discontinuation in approximately 1% of patients receiving APO-SOTALOL. The incidence was higher in patients presenting with sustained ventricular tachycardia/fibrillation (4.6%, n=1363), or a prior history of heart failure (7.3%, n=696). Based on a life-table analysis, the one-year incidence of new or worsened CHF was 3% in patients without a prior history and 10% in patients with a prior history of CHF. NYHA Classification was also closely associated to the incidence of new or worsened heart failure in patients receiving APO-SOTALOL (1.8% in 1395 Class I patients, 4.9% in 1254 Class II patients and 6.1% in 278 Class III or IV patients).

Conduction Disturbances: Excessive prolongation of the QT interval (>550 msec) can promote serious arrhythmias and should be avoided (see Proarrhythmia). Sinus bradycardia (heart rate less than 50 bpm) occurred in 13% of patients receiving Sotalol hydrochloride in clinical trials, and led to discontinuation in about 3% of patients. Bradycardia itself increases the risk of torsade de pointes. Sinus pause, sinus arrest and sinus node dysfunction occur in less than 1% of patients. The incidence of 2nd- or 3rd-degree AV block is approximately 1%.

Recent Myocardial Infarction: Caution should be exercised when APO-SOTALOL is given to patients with recent myocardial infarction. Experience in the use of sotalol hydrochloride in the early stage of recovery from acute myocardial infarction is limited and, at least at high initial doses, not reassuring. In the first 2 weeks following acute myocardial infarction, particular caution is advised. Careful dose titration is especially important, particularly in patients with impaired ventricular function.

In a double-blind, placebo-controlled secondary prevention trial in 1456 post-infarction patients who did not necessarily have ventricular arrhythmias, Sotalol hydrochloride was given as a non-titrated dose of 320 mg once daily. The results did not suggest an adverse effect on survival;

however, there was a suggestion of excess mortality (3% on sotalol hydrochloride versus 2% on placebo) during the first ten days of the trial. In another trial, where high doses of sotalol hydrochloride (320 mg twice daily) were given to a small number of high-risk post-infarction patients (n=17 randomized to APO-SOTALOL), there were four fatalities and three serious hemodynamic/electrical adverse events within two weeks of initiating sotalol hydrochloride.

Abrupt Cessation of Therapy: Patients should be warned against abrupt interruption or discontinuation of APO-SOTALOL. Hypersensitivity to catecholamines has been observed in patients withdrawn from beta blocker therapy. There have been occasional reports of severe exacerbation of angina pectoris, ventricular arrhythmias and in some cases myocardial infarction following abrupt discontinuation of beta blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, it is prudent when discontinuing chronically administered APO-SOTALOL, particularly in patients with ischemic heart disease, to carefully monitor the patient and to discontinue APO-SOTALOL in a stepwise manner or consider the temporary use of an alternate beta-blocker if appropriate. If possible, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully observed. The same frequency of administration should be maintained. If angina markedly worsens or acute coronary insufficiency develops, appropriate therapy should be instituted promptly. Because coronary artery disease is common and may be unrecognized in patients receiving

APO-SOTALOL, abrupt discontinuation in patients with arrhythmias may unmask latent coronary insufficiency.

Anaphylaxis: While taking beta blockers, patients with a history of anaphylactic reactions to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic.

There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacologic effects of the beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other hand, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation ofbronchospasm.

Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Non-Allergic Bronchospasm (e.g. Chronic Bronchitis and Emphysema): **Patients with bronchospastic diseases should in general not receive beta-blockers**. It is prudent, if APO-SOTALOL is to be administered, to use the smallest effective dose, so that inhibition of bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors may be minimized.

Sick Sinus Syndrome: APO-SOTALOL should be used only with extreme caution in patients with sick sinus syndrome associated with symptomatic arrhythmias, because it may cause sinus bradycardia, sinus pauses or sinus arrest.

Skin Rashes and Oculomucocutaneous Syndrome: Various skin rashes and conjunctival xerosis have been reported with beta blockers, including sotalol hydrochloride. A severe syndrome (oculomucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic-blocking agent (practolol). This syndrome has not been observed with sotalol hydrochloride. Physicians, however, should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Thyrotoxicosis: In patients with thyrotoxicosis, APO-SOTALOL may mask the clinical signs of hyperthyroidism or its complications and give a false impression of improvement. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of APO-SOTALOL which might be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

PRECAUTIONS

Renal Impairment: Renal function tests should be carried out at appropriate intervals. Caution should be observed in patients with impaired renal function since APO-SOTALOL (sotalol hydrochloride) is eliminated mainly via the kidneys through glomerular filtration and to a small degree by tubular secretion. There is a direct relationship between renal function, as measured by serum creatinine or creatinine clearance, and the elimination rate of APO-Sotalol. Guidance for dosing in conditions of renal impairment can be found under DOSAGE AND ADMINISTRATION.

Diabetes: APO-SOTALOL should be administered with caution to patients with history of spontaneous hypoglycemia or to patients with diabetes (especially labile diabetes) receiving insulin or oral hypoglycemic agents. Beta-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia; e.g. tachycardia.

Anesthesia: It is not advisable to withdraw beta-adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using APO-SOTALOL with anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1 to 2 mg i.v.).

Some patients receiving beta-adrenoceptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting the heart and maintaining the heart beat has also been reported.

In emergency surgery, since APO-Sotalol is a competitive antagonist at beta-adrenoceptor sites, its effects may be reversed, if required, by sufficient doses of such agonists as isoproterenol or noradrenaline.

Use in Pregnancy: There are no studies in pregnant women. Sotalol hydrochloride has been shown to cross the placenta, and is found in amniotic fluid. There has been a report of subnormal birth weight with sotalol hydrochloride. Therefore, APO-SOTALOL should be used during pregnancy only if the potential benefit outweighs the potential risk.

Use in Nursing Mothers: APO-SOTALOL has been reported to be present in human milk. Because of the potential for adverse reactions from APO-SOTALOL in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in Children: The safety and effectiveness of APO-SOTALOL in children have not been established.

Drug Interactions

Antiarrhythmics: Class Ia antiarrhythmic drugs, such as disopyramide, quinidine and procainamide, and Class III drugs (e.g. amiodarone) are not recommended as concomitant therapy with APO-SOTALOL because of their potential to prolong refractoriness (see WARNINGS). There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics. Additive Class II effects would also be anticipated with the use of other beta-blocking agents concomitantly with APO-SOTALOL.

Drugs Prolonging the QT Interval: APO-SOTALOL should also be given with extreme caution in conjunction with other drugs known to prolong the QT interval, such as Class I and Class III antiarrhythmics, phenothiazines, tricyclic antidepressants, terfenadine, astemizole, erythromycin, lithium and liquid protein diets.

Digoxin: Single and multiple doses of sotalol hydrochloride do not significantly affect serum digoxin levels. Proarrhythmic events were more common in sotalol hydrochloride treated patients also receiving digoxin. It is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in the patients receiving digoxin.

Calcium Blocking Drugs: APO-SOTALOL should be administered with caution in conjunction with calcium blocking drugs because of possible synergistic impairment of atrioventricular conduction and of ventricular function. Additionally, concomitant use of these drugs may have additive effects on blood pressure, possibly leading to hypotension.

Catecholamine-Depleting Agents: Concomitant use of catecholamine-depleting drugs, such as reserpine and guanethidine, with a beta-blocker may produce an excessive reduction of resting sympathetic nervous tone. Patients treated with APO-SOTALOL plus a catecholamine-depletor should therefore be closely monitored for evidence of hypotension and/or marked bradycardia, which may produce syncope.

Insulin and Oral Hypoglycemics: Hypoglycemia and hyperglycemia may occur and the dosage of antidiabetic drugs should be adjusted accordingly (see PRECAUTIONS, Diabetes).

Clonidine: Beta-blocking drugs may potentiate the rebound hypertension sometimes observed after discontinuation of clonidine; therefore, the beta-blocker should be discontinued several days before the gradual withdrawal of clonidine.

Beta-2-Receptor Stimulants: Beta-agonists such as salbutamol, terbutaline and isoprenaline may have to be administered in increased dosages when used concomitantly with APO-SOTALOL.

ADVERSE REACTIONS

During premarketing trials, 3186 patients with cardiac arrhythmias (1363 with sustained ventricular tachycardia) received oral sotalol hydrochloride, of whom 2451 received the drug for at least two weeks. The most important adverse effects are torsade de pointes and other serious new ventricular arrhythmias (see WARNINGS), occurring at rates of almost 4% and 1%, respectively, in the VT/VF population. Overall, discontinuation because of unacceptable side effects was necessary in 17% of all patients in clinical trials, and in 13% of patients treated for at least two weeks. The most common adverse reactions leading to discontinuation of sotalol hydrochloride are as follows: fatigue 4%, bradycardia (<50 bpm) 3%, dyspnea 3%, proarrhythmia 3%, asthenia 2% and dizziness 2%. Occasional reports of elevated serum liver enzymes have occurred with APO-Sotalol therapy but no cause and effect relationship has been established.

One case of peripheral neuropathy which resolved on discontinuation of APO-Sotalol and recurred when the patient was rechallenged with the drug was reported in an early dose tolerance study. Elevated blood glucose levels and increased insulin requirements can occur in diabetic patients.

The following table lists as a function of dosage the most common (incidence of 2% or greater) adverse effects, regardless of relationship to therapy and the percent of patients discontinued due to the event, as collected from clinical trials involving 1292 patients with sustained VT/VF.

Incidence (%) of Adverse Events and Discontinuations							
Body System	Daily Dose						
	160 mg (n=832)	240 mg (n=263)	320 mg (n=835)	480 mg (n=459)	640 mg (n=324)	Any Dose* (n=1292)	%Patients Discont. (n=1292)
BODY AS A WHOLE							
Infection	1	2	2	2	3	4	<1
Fever	1	2	3	2	2	4	<1
Localized pain	1	1	2	2	2	3	<1
CARDIOVASCULAR							
Dyspnea	5	8	11	15	15	21	2
Bradycardia	8	8	9	7	5	16	2
Chest pain	4	3	10	10	14	16	<1
Palpitation	3	3	8	9	12	14	<1
Edema	2	2	5	3	5	8	1
ECG abnormal	4	2	4	2	2	7	1
Hypotension	3	4	3	2	3	6	2

Incidence (%) of Adverse Events and Discontinuations							
Body System	Daily Dose						
	160 mg (n=832)	240 mg (n=263)	320 mg (n=835)	480 mg (n=459)	640 mg (n=324)	Any Dose* (n=1292)	%Patients Discont. (n=1292)
Proarrhythmia	<1	<1	2	4	5	5	3
Syncope	1	1	3	2	5	5	1
Heart failure	2	3	2	2	2	5	1
Presyncope	1	2	2	4	3	4	<1
Peripheral vascular disorder	1	2	1	1	2	3	<1
Cardiovascular disorder	1	<1	2	2	2	3	<1
Vasodilation	1	<1	1	2	1	3	<1
AICD discharge	<1	2	2	2	2	3	<1
Hypertension	<1	1	1	1	2	2	<1
NERVOUS							
Fatigue	5	8	12	12	13	20	2
Dizziness	7	6	11	11	14	20	1
Asthenia	4	5	7	8	10	13	1
Lightheaded	4	3	6	6	9	12	1
Headache	3	2	4	4	4	8	<1
Sleep problem	1	1	5	5	6	8	<1
Perspiration	1	2	3	4	5	6	<1
Altered consciousness	2	3	1	2	3	4	<1
Depression	1	2	2	2	3	4	<1
Paresthesia	1	1	2	3	2	4	<1
Anxiety	2	2	2	3	2	4	<1
Mood change	<1	<1	1	3	2	3	<1
Appetite disorder	1	2	2	1	3	3	<1
Stroke	<1	<1	1	1	<1	1	<1
DIGESTIVE							
Nausea/vomiting	5	4	4	6	6	10	1
Diarrhea	2	3	3	3	5	7	<1
Dyspepsia	2	3	3	3	3	6	<1
Abdominal pain	<1	<1	2	2	2	3	<1
Colon problem	2	1	1	<1	2	3	<1
Flatulence	1	<1	1	1	2	2	<1
RESPIRATORY							
Pulmonary problem	3	3	5	3	4	8	<1
Upper respiratory tract	1	1	3	4	3	5	<1
problem Asthma	1	<1	1	1	1	2	<1
UROGENITAL							
Genitourinary disorder	1	0	1	1	2	3	<1
Sexual dysfunction	<1	1	1	1	3	2	<1
METABOLIC							
Abnormal lab value	1	2	3	2	1	4	<1
Weight change	1	1	1	<1	2	2	<1
MUSCULOSKELETAL							
Extremity pain	2	2	4	5	3	7	<1
Back pain	1	<1	2	2	2	3	<1

Incidence (%) of Adverse Events and Discontinuations							
Body System	Daily Dose						
	160 mg (n=832)	240 mg (n=263)	320 mg (n=835)	480 mg (n=459)	640 mg (n=324)	Any Dose* (n=1292)	%Patients Discont. (n=1292)
SKIN AND APPENDAGES Rash	2	3	2	3	4	5	<1
HEMATOLOGIC Bleeding	1	<1	1	<1	2	2	<1
SPECIAL SENSES Visual problem	1	1	2	4	5	5	<1
*Because patients are counted at each dose level tested, the "Any Dose" column cannot be determined by adding across the doses.							

Potential Adverse Effects

Marketing experience with sotalol hydrochloride showed an adverse experience profile similar to that described above from clinical trials. Voluntary reports since introduction include rare reports (less than one report per 10,000 patients) of: emotional lability, slightly clouded sensorium, incoordination, vertigo, paralysis, thrombocytopenia, eosinophilia, leukopenia, photosensitivity reaction, fever, pulmonary edema, hyperlipidemia, myalgia, pruritus, reversible alopecia.

Additional adverse effects have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia; and acute reversible syndrome characterized by disorientation for time and place, short-term memory loss and decreased performance on neuropsychometrics.

Allergic: Fever, combined with aching and sore throat, laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenia purpura.

Gastrointestinal: Mesenteric arterial thrombosis; ischemic colitis.

Other: Peyronie's disease, Raynaud's phenomenon.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Intentional or accidental overdosage with sotalol hydrochloride has rarely resulted in death. The most common signs to be expected are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycemia. In cases of massive intentional overdosage (2 - 16 grams) with sotalol hydrochloride, the following clinical findings were seen: hypotension, bradycardia, prolongation of QT interval, torsade de pointes, ventricular tachycardia, and premature ventricular complexes. If overdosage occurs, therapy with sotalol hydrochloride should be discontinued. Close monitoring of the electrocardiogram in patients with suspected APO-

SOTALOL intoxication is essential. Because of the lack of protein binding, hemodialysis is useful for reducing APO-SOTALOL plasma concentrations. Patients should be carefully observed until QTc intervals are normalized. Every effort should be made to correct promptly metabolic and electrolyte imbalances which might contribute to the initiation of ventricular arrhythmias (see WARNINGS).

If required, the following therapeutic measures are suggested:

1) Bradycardia: Atropine, another anticholinergic drug, a beta-adrenergic agonist or transvenous cardiac pacing.
2) Heart Block (second and third degree): Isoproterenol or transvenous cardiac pacemaker.
3) Congestive Heart Failure: Conventional therapy.
4) Hypotension: (Depending on associated factors) epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis (see PRECAUTIONS).
5) Bronchospasm: Aerosolized beta-2-receptor stimulant or aminophylline.
6) Hypoglycemia: Intravenous glucose.
7) Torsade de pointes: Epinephrine, magnesium sulphate, transvenous cardiac pacing, DC cardioversion.

It should be remembered that sotalol hydrochloride is a competitive antagonist of isoproterenol and, hence, large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of APO-SOTALOL. However, the complications of excess isoproterenol should not be overlooked.

DOSAGE AND ADMINISTRATION

APO-SOTALOL (sotalol hydrochloride), when used for the treatment of documented life-threatening ventricular arrhythmias, should be initiated and dose increased in a hospital with facilities for cardiac rhythm monitoring and assessment (see INDICATIONS AND CLINICAL USE). APO-SOTALOL should be administered only after appropriate clinical assessment, and the dosage of APO-SOTALOL must be individualized on the basis of therapeutic response and tolerance. The usefulness of monitoring plasma level for optimization of therapy has not been established. Proarrhythmic events can occur not only at the initiation of therapy, but also with each upward dosage adjustment.

Dosage of APO-SOTALOL should be adjusted gradually, allowing 2 - 3 days between dosing increments in order to attain steady-state plasma concentrations and to allow monitoring of QT intervals. Graded dose adjustment will help prevent the use of doses which are higher than necessary to control the arrhythmia. The recommended initial dose is 80 mg twice daily. If needed, this dose may be increased, after appropriate evaluation, to 240 or 320 mg/day. In most patients, a therapeutic response is obtained at a total daily dose of 160 to 320 mg/day, given in two divided doses. Some patients with life-threatening refractory arrhythmias may require doses as high as 480-640 mg/day; however, these doses should only be prescribed when the potential benefit outweighs the increased risk of adverse events, in particular proarrhythmias. Because of the long elimination half-life of sotalol hydrochloride, dosing on more than a twice daily regimen is not usually necessary.

Patients experiencing bradycardia or hypotension on initial administration of APO -SOTALOL should be removed from therapy; APO-SOTALOL may be later reintroduced at a lower dose. A dose reduction may also be advisable to alleviate symptoms of weakness and dizziness in cases where blood pressure remains low after more than a month of therapy.

Renal Impairment: Because APO-SOTALOL is excreted predominantly in urine and its elimination half-life is prolonged in conditions of renal impairment, a longer duration of dosing is required to reach steady state. The dosing interval of APO-SOTALOL should then be modified, when creatinine clearance is <60 mL/min., as shown in the following table:

Creatinine Clearance (mL/min)	Dosing Interval (hours)
>60	12
30 - 60	24
10 - 30	36 - 48
<10	Dose should be individualized

Dose increases in renal impairment should only be done after administration of at least 5 or 6 doses at appropriate intervals.

Transfer to and from APO-SOTALOL: Based on theoretical considerations rather than experimental data, the following suggestion is made: when transferring patients from another antiarrhythmic drug to APO-SOTALOL or from APO-SOTALOL to another antiarrhythmic agent, allow at least 3 to 4 half-lives to elapse for the drug being discontinued before starting the alternative drug at the usual dosage. In patients where withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

PHARMACEUTICAL INFORMATION

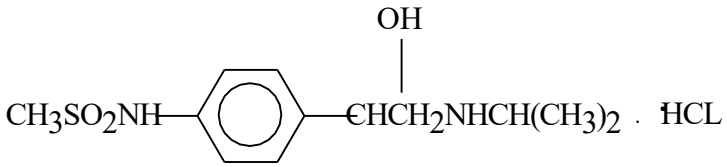
Drug Substance

Proper Name: Sotalol hydrochloride

Chemical Name(s): 1) Methanesulfonamide, *N*-[4-[1-hydroxy-2-[(1-methylethyl)-amino]ethyl]phenyl]-, monohydrochloride

2) 4'-[1-Hydroxy-2-(isopropyl-amino)ethyl]-methane-sulfonanilide monohydrochloride

Structural Formula:



Molecular Formula: $C_{12}H_{20}N_2O_3S \bullet HCl$

Molecular Weight: 308.82

Description: Sotalol hydrochloride is a white to pale cream, crystalline, odourless powder which has a melting point of 212 - 214ºC. It is freely soluble in water and methanol, and sparingly soluble in chloroform.

Composition
The non-medicinal ingredients in APO-SOTALOL are colloidal silicon dioxide, dextrates, indigotine (Blue #2), magnesium stearate and methylcellulose.

Stability and Storage Recommendations
Store at room temperature (15 to 30ºC). Protect from light.

AVAILABILITY OF DOSAGE FORMS

Each blue, capsule-shaped, biconvex tablet, identified "80" on one side and scored on the other, contains 80 mg of sotalol hydrochloride. Available in bottles of 100, 250, 500 and 1000.

Each blue, capsule-shaped, biconvex tablet, identified "160" on one side and scored on the other, contains 160 mg of sotalol hydrochloride. Available in bottles of 100, 250, 500 and 1000.

PHARMACOLOGY

In vitro, sotalol hydrochloride antagonized the chronotropic and inotropic effects of isoproterenol on isolated spontaneously beating atria and perfused cat heart, and antagonized the relaxant action of isoproterenol on the spontaneous contractions of the "diestrus" rat uterus, and the intrinsic tonus and histamine-induced spasms of the guinea pig.

In anesthetized dogs, sotalol hydrochloride administered intravenously had a negative inotropic

and chronotropic action.

Sotalol hydrochloride completely blocked the changes in heart rate, cardiac output, left ventricular work and total peripheral resistance induced by isoproterenol and had decreasing effects on respiration, blood pressure and heart rate similar to propranolol.

Sotalol hydrochloride reduced the mortality rate in dogs with ligation of a coronary artery, which was thought to be due to beta-blockade, suppressed the actinine, coronary artery ligation and hydrocarbon-epinephrine-induced arrhythmias and suppressed atrial flutter and restored normal sinus rhythm.

The ECG is not changed with the exception of a minor prolongation of the PR interval. Sotalol hydrochloride will inhibit isoproterenol-induced tachycardia and exercise tachycardia. In patients receiving right and left heart catheterization, the drug produced a significant reduction in heart rate and cardiac output, but stroke volume was unchanged. Systemic arterial and pulmonary pressures were not significantly altered, but indices of myocardial function were reduced. Nine patients with angina pectoris, studied at a constant treadmill speed, showed an increase in exercise time after sotalol hydrochloride i.v. 0.5 mg/kg of 80 to 165 seconds.

Sotalol hydrochloride has no local anesthetic action on rabbit eye or guinea pig skin at concentrations ranging from 0.1 to 6.4%. The intravenous injection of sotalol hydrochloride in anesthetized dogs caused reduction in pulmonary blood flow, increase in pulmonary vascular resistance and interference in the increase of pulmonary flow in response to isoproterenol, anoxia and electrical stimulation of thoracic sympathetic nerve.
In 13 patients suffering from obstructive lung disease, the administration of sotalol hydrochloride provoked a significant increase of the airway resistance and a decrease of the FEV. APO-Sotalol does not alter intraocular pressure.

TOXICOLOGY

Acute Toxicity

Species	Sex	No. of Animals	Route	LD_{50} (mg/kg)	No. of Deaths
Mice	M	50	Oral	2600	15
	M	130	i.p.	670 645	36
	M	40	i.v.	174	19
Rats	M	90	Oral	3450	13
	M	30	i.p.	680	-
Rabbits	M&F	12	Oral	1000	6
	M&F	12	i.v.	78	3
Dogs	M&F	6	Oral	50*	-
	M&F	18	i.p.	330	4
	M&F	24	i.v.	240	5
*Emesis occurred at doses of 100 and 200 mg/kg; LD_{50} could not be determined					

Signs of toxicity were: ataxia, labored respiration, loss of righting reflex, depression, hypoactivity, asphyxial movements and convulsions.

The following signs were also reported in some species: ptosis, increased respiratory depth, Straub's tail reaction, head and body shaking, emesis, bradycardia, cyanosis, relaxed nictitating membrane, moderate tearing, watery stools, weak heart beat, profuse salivation, coarse tremors and piloerection.

Chronic Toxicity

Species	Sex	Route of Administration	Dosage Regimen	Time Period	Toxicity Signs
Mice	F	Oral	500 mg/ kg/day	6 months	None
Rats	M&F	Oral	0,50,250, 1250 mg/ kg/day	1 year	Ataxia, depression, slightly depressed growth and food efficiency, increased spleen weight
Rats	M&F	Oral	0,75,275, 975 or 1000 mg/kg/day	1 year	Decrease in body weight gain (dose-related), increases in heart dimensions of male rats and cartilagenous metaplasia in heartsections
Dogs	M&F	Oral	0,5,15,45, 60 or 70 mg/kg/day	1 year	Decrease in heart rate (dose-related)

Reproductive Studies

The oral administration of sotalol hydrochloride of 500 mg/kg/day on days 3, 5, 7, 8, 10 and 12 of gestation in pregnant mice and of 100 mg/kg on day 6 through 16 in pregnant rabbits had no effect on the incidence of successful pregnancies, litter size, incidence of stillborn, weight of newborn, growth of newborn to weaning and post-natal survival.

Male rats fed 20 or 142 mg/kg of sotalol hydrochloride for 70 weeks exhibited no drug related decrease in reproductive performance.

Oral administration of 1000 mg/kg to male and female rats prior to mating had no adverse effect upon the fertility of female rats, the post-natal survival and development of the offspring. Female rats had fewer pups per litter than control rats. No evidence of teratogenesis was noted.

The continuous administration of sotalol hydrochloride to pregnant rats (20, 140 or 1000 mg/kg) and to pregnant rabbits (100, 150 or 225 mg/kg) during the critical period of organogenesis for each species had no teratogenic or embryotoxic effect on their offspring. In rats, 1000 mg/kg/day of sotalol hydrochloride increased the number of early resorptions, while at 14 times the maximum dose, no increase in early resorptions was noted.

Tumorigenic Tests

Sotalol hydrochloride, orally administered to mice at doses of 0, 100, 300 or 600 mg/kg/day for a period of 18 months in two different studies, did not show statistical differences in total or specific tumours when compared to control groups.

Sotalol hydrochloride, orally administered to rats at doses of 0, 137, or 275 mg/kg/day for a period of 18 months did not show statistical differences in the incidence of neoplasms, when compared to control groups.

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PRODUCT MONOGRAPH

PrMIDODRINE

Midodrine Hydrochloride Tablets

2.5 mg and 5 mg

Vasopressor

AA PHARMA INC.
100 King Street West, Suite 5700
Toronto, Ontario
M5X 1C7

Control #: 138681

DATE OF PREPARATION:
May 26, 2010

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[Pr]MIDODRINE
Midodrine Hydrochloride Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet / 2.5 mg, 5 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Because midodrine hydrochloride can cause marked elevation of supine blood pressure, it should only be used in patients whose lives are considerably impaired despite standard clinical care including non-pharmacologic treatment, plasma volume expansion and lifestyle alterations. The use of midodrine hydrochloride in the management of symptomatic orthostatic hypotension is based primarily on a change in a surrogate endpoint of effectiveness, an increase in systolic blood pressure measured one minute after standing, a surrogate endpoint considered likely to correspond to clinical benefits. At present, however, clinical benefits of midodrine hydrochloride, principally improved ability to carry out activities of daily life, have not been verified.

MIDODRINE (midodrine hydrochloride) may be used to attenuate symptoms of chronic orthostatic hypotension due to autonomic failure in patients with Bradbury-Eggleston syndrome, Shy-Drager syndrome, diabetes mellitus disease and Parkinson's disease.

The initiation and up-titration of midodrine therapy should be undertaken under close medical supervision in a controlled clinical setting (see DOSAGE AND ADMINISTRATION).

The safety of midodrine hydrochloride in patients with orthostatic hypotension due to etiology other than those named above has not been established and its use is, therefore, not recommended.

Geriatrics (>65 years of age): MIDODRINE can be used in patients 65 years or older who have adequate renal and liver function.

Pediatrics (<18 years of age): The use of MIDODRINE is not recommended in children.

CONTRAINDICATIONS

MIDODRINE (midodrine hydrochloride) is contraindicated in patients with:

- pre-existing persistent and excessive supine hypertension,
- severe organic heart disease,
- acute renal disease,
- urinary retention,
- pheochromocytoma,
- thyrotoxicosis or
- known hypersensitivity to midodrine.

WARNINGS AND PRECAUTIONS

Supine Hypertension: The most potentially serious adverse reaction associated with midodrine therapy is marked elevation of supine arterial blood pressure (supine hypertension), which, if sustained, may cause stroke, myocardial infarction, congestive heart failure, renal insufficiency or similar disorders which individually or collectively may be fatal. Symptoms of supine hypertension are more frequently detected at the initiation of midodrine therapy and during the titration period. It is essential to monitor supine and sitting blood pressures in patients maintained on midodrine.

Control of supine blood pressure has been obtained by an adjustment in midodrine dosage with or without a 45-degree elevation of the patient's head. If supine hypertension persists, treatment with midodrine should be discontinued, and appropriate therapy (e.g., phentolamine, a specific antagonist of midodrine pressor activity) instituted immediately.

Systolic hypertension of about 200 mm Hg were seen overall in about 11.8% of patients treated with 10 mg of midodrine hydrochloride, in 4 controlled clinical studies. Systolic elevation of this degree were most likely to be observed in patients with relatively elevated pre-treatment blood pressure (mean 170 mm Hg). There is no experience in patients with initial supine systolic pressure above 180 mm Hg as those patients were excluded from the clinical trials. Use of MIDODRINE in such patients is not recommended. Sitting blood pressures were also elevated by midodrine hydrochloride therapy and it is, therefore, essential to monitor supine and sitting blood pressures in patients maintained on MIDODRINE (see DOSAGE AND ADMINISTRATION).

To minimize the incidence of supine hypertension, instruction how to initiate midodrine therapy should strictly be followed (see DOSAGE AND ADMINISTRATION). Patients should be cautioned to report symptoms of supine hypertension immediately. Symptoms may include cardiac awareness, pounding in the ears, headache, blurred vision, etc. If these occur, the patient should discontinue the drug and consult with the prescribing physician.

Bradycardia: Bradycardia may occur after MIDODRINE tablets administration, primarily due to vagal reflex. Caution should be exercised when MIDODRINE is used concomitantly with cardiac glycosides (such as digitalis), psychopharmacologic agents, beta blockers or other agents which directly or indirectly reduce heart rate. Patients who experience bradycardia should be told to report immediately any signs or symptoms suggesting bradycardia (pulse slowing, increased dizziness, syncope, cardiac awareness) and to take no more drug until they have consulted with the prescribing physician.

Patients with Urinary Retention: MIDODRINE is contraindicated in patients with urinary retention.

Cardiac Arrhythmias: MIDODRINE should not be administered in the presence of uncorrected tachyarrhythmias.

General: The potential for supine and sitting hypertension should be evaluated at the beginning of midodrine therapy. Supine hypertension can often be controlled by an adjustment in midodrine dosage and/or preventing the patient from becoming fully supine, i.e., sleeping with the head of the bed elevated. The patient should be cautioned to report symptoms of supine hypertension immediately. Symptoms may include cardiac awareness, pounding in the ears, headache, blurred vision, etc. The patient should be advised to discontinue the medication immediately if supine hypertension persists.

Patients with Diabetes Mellitus: Midodrine should be used with caution in orthostatic hypotensive patients who are also diabetic, as well as those with a history of visual problems who are also taking fludrocortisone acetate, which is known to cause an increase in intraocular pressure and glaucoma.

Patients with Renal Impairment: Midodrine has not been studied in patients with renal impairment. Because desglymidodrine is eliminated via the kidneys, and higher blood levels would be expected in such patients, midodrine should be used with caution in patients with renal impairment, with a starting dose not higher than 2.5 mg (see DOSAGE AND ADMINISTRATION) and the patient's blood pressure should be monitored closely. Renal function should be assessed prior to initial use of midodrine and when appropriate during therapy.

Patients with Hepatic Impairment: Midodrine has not been studied in patients with hepatic impairment. Midodrine should be used with caution in patients with hepatic impairment, as the liver has a role in the metabolism of midodrine.

Urinary Retention: Midodrine may induce an increase in the tone of the internal sphincter of the urinary bladder which may lead to urinary retention. Midodrine also may effect the bladder trigone which may result in a delayed response to bladder filling. Initial signs of urinary retention are manifested clinically as hesitancy or change in frequency of micturition. Patients should be told to report promptly any indication of urinary retention (e.g., hesitancy or frequency of micturition) which may be a sign of urinary retention.

Midodrine should be used with caution in patients with urinary tract outflow obstruction, neurogenic bladder or similar conditions, since midodrine and desglymidodrine are eliminated by the kidneys and accumulation may occur in such patients.

Use in Children: Safety and effectiveness in children have not been established.

Use in Pregnancy: No teratogenic effects have been observed in studies in animals. At very high doses (20 mg/kg/day) the drug was toxic to dams and fetal loss occurred. There are no data on the use of midodrine on pregnant women. Therefore, midodrine should be used during pregnancy only when the benefit to the mother exceeds the possible harm to the fetus.

Nursing Mothers: It is not known if midodrine is excreted in human milk. Caution should be exercised when midodrine is administered to nursing mothers.

Laboratory Tests: Evaluation of the patient should include assessment of renal and hepatic function prior to initiation of therapy, and during treatment, when appropriate.

ADVERSE REACTIONS

Midodrine hydrochloride has been evaluated for safety in Phase III clinical trials in 938 patients with symptomatic orthostatic hypotension due to autonomic failure (Bradbury-Eggleston, 26.7%; Shy-Drager Syndrome, 17.8%; Parkinson's disease, 11%; diabetes mellitus, 21.2%; other conditions, 23.3%). There were 245 patients who received midodrine hydrochloride in double-blinded, placebo-controlled trials.

In the placebo-controlled studies, adverse events regardless of causality were reported in 40.4% of the patients on midodrine 10 mg t.i.d. compared to 18.6% on placebo.

In placebo-controlled trials, the rate of discontinuation of patients on midodrine 10 mg t.i.d. due to adverse events, regardless of causality, was 15.8% compared to 0% on placebo. Discontinuation due to urinary disturbance, pilomotor reactions and supine hypertension were the reasons for premature withdrawal that were more common on midodrine.

In patients treated with midodrine in which a causal relationship could not be excluded, there was one case of a serious adverse reaction reported, i.e. central retinal vein occlusion.

The most frequent (>2%) adverse events in placebo-controlled trials were supine and sitting hypertension; paraesthesia and pruritus, mainly of the scalp; goose bumps; chills; urinary urge; urinary retention and urinary frequency.

The incidence of these events in a 3-week placebo-controlled trial is shown in the following table.

	PLACEBO	MIDODRINE
Adverse Event	**% of patients**	**% of patients**
Paraesthesia[1]	4.5	18.3
Piloerection	0	13.4
Dsyuria[2]	0	13.4
Pruritus[3]	2.3	12.2
Supine hypertension[4]	0	7.3
Chills	0	4.9
Pain[5]	0	4.9
Rash	1.1	2.4

[1] Includes paraesthesia, paraesthesia of scalp and hyperesthesia of skin.
[2] Includes dysuria, increased urinary frequency, impaired urination, urinary retention (6%), urinary urgency.
[3] Includes scalp pruritus (11%).
[4] Includes patients with increased supine hypertension (2.4%).
[5] Includes abdominal pain and pain increase.

In the 938 patients treated in controlled and uncontrolled trials, the following adverse events, regardless of causality, occurred at a frequency greater than 0.5% or occurred at a lower rate but were potentially important: asthenia, chills, dizziness, dyspepsia, dyspnea, hair disease, headache, hypertension, nausea, nervousness, pain, paraesthesia, paraesthesia scalp, piloerection, vasodilation, pruritus, pruritus scalp, rash, supine hypertension, urine retention, urine urgency.

The most potentially serious adverse reaction associated with midodrine therapy is supine hypertension. The feelings of paraesthesia, pruritus, piloerection, and chills are pilomotor reactions associated with the action of midodrine on the alpha-adrenergic receptors of the hair follicles. Feelings of urinary urgency, retention, and frequency are associated with the action of midodrine on the alpha-receptors of the bladder neck.

Laboratory Abnormalities: There were no clinical significant changes to laboratory parameters.

DRUG INTERACTIONS

Digitalis: Cardiac glycosides may enhance or precipitate bradycardia, A.V. block or arrhythmia when administered concomitantly with midodrine.

Sympathomimetic agents: The use of drugs that stimulate alpha-adrenoceptors (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine or dihydroergotamine) may enhance or potentiate the pressor effects of midodrine. Therefore, midodrine should not be used concomitantly with vasoconstrictor sympathomimetic agents and the patient should be warned not to use over-the-counter preparations containing these drugs.

Sympatholytic agents: Alpha-adrenoceptor antagonists such as phentolamine, prazosin, doxazosin and labetalol can inhibit the vasopressor effect of midodrine.

Corticosteroids: Patients on salt-retaining steroids (e.g., fludrocortisone), with or without salt supplementation, may experience an excessive pressor effect after midodrine therapy, especially in the supine posture. The possibility of hypertensive effects with midodrine can be minimized by either reducing the dose of fludrocortisone or decreasing the salt intake prior to initiation of treatment with midodrine.

Potential for Drug Interactions: It appears possible, although there is no supporting experimental evidence, that the high renal clearance of desglymidodrine (a base) is due to active tubular secretion by the base-secreting system also responsible for the secretion of such drugs as metformin, cimetidine, ranitidine, procainamide, triamterene, flecainide, and quinidine. Thus there may be a potential for drug-drug interactions with these drugs.

DOSAGE AND ADMINISTRATION

Treatment with MIDODRINE (midodrine hydrochloride) should be started under close medical supervision in a controlled clinical setting such as in hospital, in clinic, or in the office. Hourly measurements of blood pressure (supine and sitting) should be made for 3 hours after the first dose and also the second dose of a three times daily dosage regimen. This procedure should be followed also when the dose is increased.

During the period of close medical supervision, the patient or a person living with the patient should be trained to measure blood pressure. Supine and sitting blood pressures should be measured daily for at least one month after the initiation of treatment and twice per week afterwards.

The administration of MIDODRINE should be stopped and the attending physician notified immediately, if the blood pressure in either position increases above 180/100 mm Hg.

The usual starting dose of MIDODRINE is 2.5 mg three times daily. Single doses of 2.5, 5 and 10 mg have been successfully employed. Most patients are controlled at or below 30 mg per day given in three or four divided doses. MIDODRINE can be given up to six times per day but a total daily dose of 30 mg should not be exceeded. Some patients require a morning dose that is higher than that taken later in the day. In some instances MIDODRINE has been given on a three times per day schedule as follows: 1 to 2 hours before arising in the morning, mid-morning and mid-afternoon. In order to reduce the potential for supine hypertension, it may be recommended that midodrine doses not be given after the evening meal or less than 4 hours before bedtime.

Therapy with MIDODRINE should be continued only in patients who appear to obtain symptomatic improvement during initial treatment.

The maximum recommended dose should not exceed 30 mg daily.

Dosing in children has not been studied as patients 18 years or younger were excluded from the clinical trials.

Use in the Elderly: Blood levels of midodrine and desglymidodrine were similar in patients 65 years or older versus those younger than 65 years suggesting that dosage adjustment is not necessary in elderly patients provided that their renal and liver functions are adequate.

Use in Patients with Liver and/or Renal Impairment: MIDODRINE should be used cautiously and the starting dose should not be higher than 2.5 mg (See PRECAUTIONS - Patients with Renal Impairment and Patients with Liver Impairment).

OVERDOSAGE

Symptoms of overdose could include hypertension, piloerection (goose bumps), a sensation of coldness and urinary retention. There are 2 reported cases of overdosage with midodrine hydrochloride, both in young males. One patient ingested midodrine hydrochloride drops, 250 mg, experienced systolic blood pressure of greater than 200 mm Hg, was treated with an IV injection of 20 mg of phentolamine, and was discharged the same night without any complaints. The other patient ingested 205 mg of midodrine hydrochloride (41 x 5 mg tablets), and was found lethargic and unable to talk, unresponsive to voice but responsive to painful stimuli, hypertensive and bradycardic. Gastric lavage was performed, and the patient recovered fully by the next day without sequelae.

The single doses that would be associated with symptoms of overdosage or would be potentially life-threatening are unknown. The oral LD_{50} is approximately 30 to 50 mg/kg in rats, 675 mg/kg in mice, and 125 to 160 mg/kg in dogs.

Recommended general treatment, based on the pharmacology of the drug, includes induced emesis and administration of alpha-sympatholytic drugs (e.g., phentolamine).

Desglymidodrine is dialyzable.

ACTION AND CLINICAL PHARMACOLOGY

Midodrine hydrochloride is a prodrug, that is, the therapeutic effect of orally administered midodrine is due to and directly related to its conversion after absorption to desglymidodrine which differs chemically from methoxamine only by lacking in a methyl group on the α carbon of the side chain.

Desglymidodrine is an α_1-adrenoceptor stimulant with little effect on cardiac β-adrenoceptors. The actions of desglymidodrine on the cardiovascular and other organ systems are essentially identical with those of other alpha$_1$-adrenoceptor stimulants, such as phenylephrine or methoxamine.

The most prominent effects of midodrine are on the cardiovascular system, consisting of a rise in standing, sitting and supine systolic and diastolic blood pressures in patients with orthostatic hypotension. Standing systolic pressure is increased by 15 to 30 mm Hg at 1 hour after a 10 mg dose of midodrine hydrochloride, with some effects persisting for another 2 to 3 hours. The increase in blood pressure is due almost entirely to an increase in peripheral resistance. Midodrine hydrochloride has no clinically significant effect on standing or supine pulse rate in patients with autonomic failure. It slightly decreases cardiac output and renal blood flow and increases the tone of the internal bladder sphincter and delays the emptying of the bladder.

Pharmacokinetics: After oral administration, midodrine is rapidly and almost completely absorbed, with a mean absolute bioavailability (as desglymidodrine) of 93%.

After the oral administration of 2.5 mg midodrine in a single dose to 12 volunteers, the mean peak concentration of unchanged midodrine is approximately 10 ng/mL and it occurs after 20-30 minutes, with a terminal plasma half-life of 0.4-0.5 hours. The mean plasma concentration of the active metabolite, desglymidodrine, peaks in approximately 1 hour, with a plasma half-life of approximately 3 hours after the oral administration of 2.5 mg midodrine.

Thorough metabolic studies have not been conducted, but it appears that deglycination of midodrine to desglymidodrine takes place in many tissues, and both compounds are metabolized in part by the liver. Neither midodrine nor desglymidodrine is a substrate for monoamine oxidase.

Both midodrine and desglymidodrine are quickly eliminated from the body, mostly by the kidneys. The renal clearance of desglymidodrine is approximately 385 mL/min, most, about 80%, by active secretion. The actual mechanism of active secretion has not been studied, but it is possible that it occurs by the base-secreting pathway responsible for the secretion of several other drugs that are bases (see WARNINGS AND PRECAUTIONS - Drug Interactions). Approximately 91% of the administered dose is excreted in the urine in 24 hours. Of the urinary material, 50-60% is present as desglymidodrine and approximately 2%, as non-metabolized midodrine. Unidentified breakdown products do not exceed 3.9% of the urinary material. Midodrine diffuses poorly across the blood-brain barrier.

STORAGE AND STABILITY

Store at room temperature (15-30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

MIDODRINE (midodrine hydrochloride) tablets are available in the following strengths for oral use.

MIDODRINE Tablets 2.5 mg: Each white, round tablet, scored and engraved "MID" over "2.5" on one side, contains 2.5 mg midodrine hydrochloride. Available in bottles of 100.

MIDODRINE Tablets 5 mg: Each orange, round tablet, scored and engraved "MID" over "5" on one side, contains 5 mg midodrine hydrochloride. Available in bottles of 100.

In addition to midodrine hydrochloride, each tablet contains the non-medicinal ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and starch. MIDODRINE 5 mg tablets also contain the colourant FD&C Yellow #6 Aluminum Lake 40%.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: midodrine hydrochloride

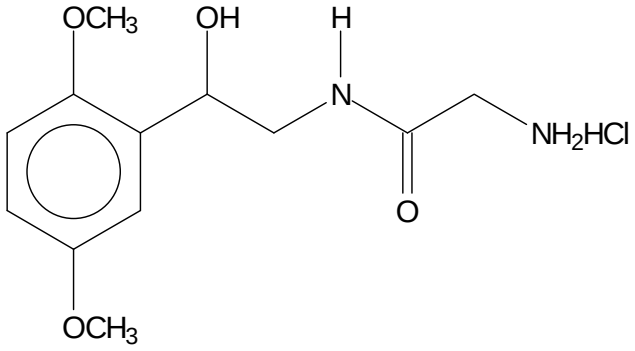
Chemical Name: (1) Acetamide, 2-amino-*N*-[2-(2,5-dimethyoxyphenyl)-2-hydroxyethyl]-, monohydrochloride, (±)-;

(2) (±)-2-Amino-N-(*β*-hydroxy-2,5-dimethoxyphenethyl)acetamide monohydrochloride

Molecular formula and molecular weight: Base: $C_{12}H_{18}N_2O_4$, 254.28

Salt $C_{12}H_{18}N_2O_4 \cdot HCl$, 290.75

Structural Formula:



Physicochemical properties: Midodrine hydrochloride is a white to off white powder. It is soluble in water and sparingly soluble in methanol. The following table contains the aqueous solubility of midrodrine over the physiological pH range.

Solvent	pH Value	Solubility (mg/mL)
H_20	6.31	>10
0.1N HCl	1.17	>10
0.01N HCl	2.09	>10
SGF	1.25	>10
Potassium Phosphate Buffer, pH 2.5	2.50	>10
Potassium Phosphate Buffer, pH 3.5	3.51	>10
Potassium Phosphate Buffer, pH 4.5	4.52	>10
Potassium Phosphate Buffer, pH 5.5	5.51	>10
Potassium Phosphate Buffer, pH 6.0	6.01	>10
Potassium Phosphate Buffer, pH 6.8	6.80	>10
Potassium Phosphate Buffer, pH 7.2	7.21	>10
Potassium Phosphate Buffer, pH 7.5	7.51	>10

pKa: 7.75 (Calculated using ACD Labs, vers. 6.0)

pH: 4.86 (1% aqueous solution)

Melting range: 192 – 193°C

Octanol/Water Partition Coefficient: -0.66 ± 0.49 (for free base)
(Calculated using ACD Labs, vers. 6.0)

CLINICAL TRIALS

In human studies, midodrine did not affect blood sugar or urea levels in hypotensive patients or did not have any adverse effects on glucose tolerance, serum lipids, insulin or uric acid in diabetic patients. During a three-week treatment with midodrine (20 mg daily), no effects were seen on plasma clotting factor, there was no activation of fibrinolysis, or effects on number and function of thrombocytes.

Midodrine has been studied in four principal controlled trials of 4 weeks, 3 weeks, 4 days and 1 day duration, respectively. All studies were randomized, double-blind trials in patients with orthostatic hypotension of any etiology and supine-to-standing fall of systolic blood pressure of at least 15 mm Hg accompanied by at least moderate dizziness/lightheadedness. Patients with preexisting sustained supine hypertension above 180/110 mm Hg were routinely excluded. In the 4-week study in 104 patients, midodrine (10 mg) significantly elevated standing systolic blood pressure 22 mm Hg (28%) compared to 3 mm Hg (4%) for the placebo group. The 2.5 mg dose elevated blood pressure 9 mm Hg (14%). The percent increase in standing systolic pressure for all midodrine doses (2.5, 5 and 10 mg) and the 5 and 10 mg doses together was significantly superior to placebo and the dose response was linear.

In a 3-week study in 170 patients, most previously untreated with midodrine, the midodrine-treated patients (10 mg t.i.d., with the last dose not later than 6 pm) had significantly higher (by about 20 mm Hg) 1-minute standing systolic pressure 1 hour after dosing (blood pressures were not measured at other times) for all 3 weeks. After week 1, midodrine-treated patients had small improvements in dizziness/lightheadedness/unsteadiness scores and global evaluations, but these effects were made difficult to interpret by a high early drop-out rate (about 25% vs 5% on placebo). Supine and sitting blood pressure rose 16/8 and 20/10 mm Hg, respectively, on average.

In a 4-day, 4-way crossover dose-response trial, single doses of 0, 2.5, 10, and 20 mg of midodrine were given to 25 patients. The 10- and 20-mg doses produced increases in standing 1-minute systolic pressure of about 30 mm Hg at 1 hour; the increase was sustained in part for 2 hours after 10 mg and 4 hours after 20 mg. Supine systolic pressure was ≥200 mm Hg in 22% of patients on 10 mg and 45% of patients on 20 mg; elevated pressures often lasted 6 hours or more.

In a 1-day study in 70 patients, after open-label midodrine, known midodrine responders received midodrine 10 mg or placebo at 0, 3, and 6 hours. One-minute standing systolic blood pressures were increased 1 hour after each dose by about 15 mm Hg and 3 hours after each dose by about 12 mm Hg; 3-minute standing pressures were increased also at 1 but not at 3 hours after dosing. There were increases in standing time seen intermittently 1 hour after dosing, but not at 3 hours.

Comparative Bioavailability

A comparative bioavailability study was performed on healthy male volunteers under fasting conditions. The rate and extent of absorption of midodrine was measured and compared following a single oral dose of MIDODRINE or AMATINE® tablets. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data
Midodrine (Dose: 1 x 5 mg) From Measured Data - Under Fasting Conditions
Based on Midodrine

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence interval (%)**
	AA–Midodrine	Amatine®†		
AUC_T (ng•h/mL)	16.5492 17.425 (27.7)	16.1900 17.098 (28.2)	102	97.8 – 107
AUC_I (ng•h/mL)	17.0043 17.844 (27.0)	16.6846 17.548 (27.4)	102	97.6 – 106
C_{MAX} (ng/mL)	21.0466 22.891 (39.1)	20.5245 22.674 (36.1)	103	88.0 - 120
T_{MAX}^{*} (h)	0.557 (44.6)	0.623 (57.6)		
$T_{½}^{*}$ (h)	0.481 (22.7)	0.513 (26.0)		

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Amatine® is manufactured by Shire Canada Inc., Canada, and was purchased in Canada.

DETAILED PHARMACOLOGY

Preclinical Studies: Intraduodenally, midodrine was effective in rats at 2.5 to 20 mg/kg. Phentolamine (5 mg/kg i.v.), an alpha-adrenergic antagonist, inhibited the pressor response to midodrine (5 mg/kg. i.v.). Other pharmacological agents including the beta-adrenergic antagonist propranolol (5 mg/kg, i.v.) and the parasympathetic antagonist atropine (5 mg/kg, i.v.), had no influence on the pressor response.

Midodrine (1 mg/kg, i.v.) and desglymidodrine (250 µg/kg, i.v.) did not significantly affect the actions of the beta-adrenergic agonist isoprenaline (0.4 µg/kg, i.v.) on systolic or diastolic pressure, dP/dT, heart rate or femoral blood flow in the anaesthetized cat.

Desglymidodrine (10^{-6} to 10^{-4} M) caused a dose-related increase in tension of isolated femoral artery and femoral vein strips from dogs while midodrine had no effect at concentrations up to 10^{-3} M. These response curves were shifted to the right in a parallel fashion by phentolamine indicating competitive antagonism.

Neither midodrine nor desglymidodrine affected acetylcholine induced bronchospasms in guinea pigs. Neither midodrine nor desglymidodrine had any significant CNS activity in the mouse.

TOXICOLOGY

Acute Toxicity: The acute toxicity of midodrine is as follows:

	LD_{50} mg/kg		
	Mouse	**Rat**	**Dog**
Intravenous	107.7	17.69	---
Intraperitoneal	199.9	25.55	---
Subcutaneous	196.6	30.18	---
Oral	675.0	32.90	126.0 – 159.0

The toxicity pattern is identical in all 3 animal species and is characterized by exophthalmus, piloerection, dyspnea, salivation and tonoclonic spasms.

Subacute Toxicity: Midodrine was given to rats (10 males and 10 females per dose) by stomach tube for up to 20 days at doses of 5, 10 and 20 mg/kg/day. Alterations of the myocardium characteristic of those produced by sympathomimetic agents, taking the form of foci of degenerative myocardial fibers and an increase in connective tissue cells, were observed and these were not clearly dose dependent. Females administered oral midodrine in doses of 5, 10 and 20 mg/kg showed fatty degeneration in the periphery of liver lobes with a decrease in glycogen content; males show cellular enlargement of the liver without fatty accumulation with cells rich in glycogen. These liver changes were dose dependent.

Chronic Toxicity: Six month toxicity studies were carried out in rats and dogs. In one experiment, Sprague-Dawley rats (10 males and 10 females per dose) were dosed orally with 1, 5 and 20 mg/kg. In a second experiment, rats (10 males and 10 females per dose) were dosed orally with 0.3 mg/kg. There was slight fatty infiltration of the liver in male rats dosed with 5 mg/kg. Changes in hepatic and plasma enzyme activities did not follow any pattern that could be related clearly to midodrine. Chronic toxicity studies for 6 months in dogs (2 males and 2 females per dose) in doses up to 12.5 mg/kg/day showed sporadic degeneration of myocardial fibers with rows of fibrocytes in the myocardium. Liver function tests remained within normal limits. Piloerection and mydriasis, initially prominent and dose dependent, gradually disappeared over several weeks of continued treatment. Vomiting occurred in the first and second week, over a period of 1-5 days. In another chronic toxicity study, dogs (3 males and 3 females per dose) were treated orally with midodrine in doses of up to 27 mg/kg/day for 6 months. The dose of 9 mg/kg/day initially produced piloerection, mydriasis and vomiting, each of which dissipated with time. At 27 mg/kg/day, mild and moderate sedation was evident and was associated with decreased food intake and weight gain. There was a significant decrease in heart and spleen weight, and a significant increase in lung, liver, and kidney weight.

Mutagenicity: No mutagenicity was seen with midodrine, according to either the Ames test, using 5 strains of *Salmonella typhimurium* (up to 1000 mg/dish), or the micronucleus test in mice (up to 50 mg/kg with *5* males and 5 females per dose).

Reproductive Studies: The effect of midodrine on reproductive function was tested by the dominant lethal assay in male CFLP mice. Oral midodrine was administered for *5* consecutive days in doses of 9, 27 and 81 mg/kg/day to male mice (20 per dose). Two days after the end of treatment, the mice were paired for one week with untreated females (120 per dose). Fetal implantation rate, litter size and post implantation loss were unaffected by treatment. Midodrine was given by gavage to Sprague-Dawley rats (20 females per dose) in dose levels of 0.1, 1.5 and 20 mg/kg/day during the sixth to the fifteenth day of pregnancy. There was no effect on pregnancy or the fetus at doses of 0.1 and 1.5 mg/kg/day. At 20 mg/kg/day, there were significant reductions in the reabsorption rate and body weight of fetuses. Dams showed significant reductions in food consumption and rate of weight gain. The effect of oral gavage of midodrine at doses of 0.1, 1.5 and 20 mg/kg/day from the sixth to the eighteenth day of pregnancy was studied in New Zealand white rabbits (10 females per dose). The progress of pregnancy and the development of the fetus was normal at the two lower doses. At a dose of 20 mg/kg/day, a post-implantation loss rate of 88.2% occurred and body weight of fetuses delivered was significantly reduced. Dams were ataxic and showed significantly reduced food intake and body weight gain.

Carcinogenicity: Long-term studies have been conducted in rats and mice at dosages of 3 to 4 times the maximum recommended daily human dose on a mg/m^2 basis, with no indication of carcinogenic effects related to midodrine.

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PART III: CONSUMER INFORMATION

[Pr]MIDODRINE
Midodrine Hydrochloride Tablets

This leaflet is part III of a three-part "Product Monograph" published when MIDODRINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MIDODRINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
MIDODRINE is used for certain patients that have low blood pressure when in a standing position. It is used in people whose living activities are severely impaired even after other treatments are used.

What it does:
Midodrine increases blood pressure by causing blood vessels to tighten.

When it should not be used:
MIDODRINE should not be taken without first consulting your doctor if you have any of the following conditions:

- High blood pressure experienced when lying down
- Severe heart disease
- Kidney disease
- Urinary difficulties
- Pheochromocytoma (a tumour of the adrenal gland that causes excess release of hormones that regulate blood pressure)
- Overactive thyroid
- Are allergic to midodrine hydrochloride or to any of the nonmedicinal ingredients listed under "What the important nonmedicinal ingredients are"

What the medicinal ingredient is:
Midodrine hydrochloride

What the important nonmedicinal ingredients are:
MIDODRINE 2.5 mg and 5 mg tablets contains the following nonmedicinal ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and starch. MIDODRINE 5 mg tablets also contain the colourant FD&C Yellow #6 Aluminum Lake 40%.

What dosage forms it comes in:
MIDODRINE is available as 2.5 mg and 5 mg tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Use of MIDODRINE can cause a marked increase in blood pressure experienced when lying down.

BEFORE you use MIDODRINE talk to your doctor or pharmacist if you:

- Have high blood pressure
- Are taking any of the medications listed in the section entitled "Interactions With This Medication"
- Have urinary difficulties
- Have an irregular heart beat
- Have low blood pressure, are diabetic or have a history of visual problems
- Have kidney or liver problems
- Are pregnant or nursing

INTERACTIONS WITH THIS MEDICATION

You should always tell your physician about all drugs you are taking or planning to take, including those obtained without a prescription.

Drugs that may interact with MIDODRINE include: digitalis glycosides (e.g. digoxin, digitoxin), adrenaline-like drugs (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine or dihydroergotamine), alpha blockers (e.g., phentolamine, prazosin, doxazosin and labetalol and steroids that cause salt-retention (e.g. fludrocortisone).

PROPER USE OF THIS MEDICATION

Usual dose:
Treatment with MIDODRINE should be started under close medical supervision so that your blood pressure can be monitored carefully. The starting dose of MIDODRINE is 2.5 mg 3 times daily or as directed by your doctor. The drug should be taken during daytime hours, when you are likely to be upright most often. MIDODRINE should not be taken after the evening meal or less than 4 hours before bedtime.

Overdose:
Seek emergency medical attention if an overdose of this medication is suspected.

Symptoms of a midodrine overdose may include increased blood pressure (heart pounding or slower heartbeat, pounding sensation in your ears, headache or blurred vision), goose bumps, a feeling of being cold and difficulty urinating.

Missed Dose:
If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of MIDODRINE are: High blood pressure experienced when sitting or lying down; Tingling or itching of the skin, mainly of the scalp; Goose bumps; Chills; Urinary problems; Abnormal loss of strength; Dizziness; Pain in the upper area of the stomach; Hair disease; Headache; Shortness of breath; Nausea; Nervousness; Pain; Rash

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	High blood pressure experienced when lying down		✔	✔
Uncommon	Abnormal heartbeat		✔	✔
Uncommon	Loss of vision (Central retinal vein occlusion)		✔	✔
Uncommon	Increased dizziness/faintness		✔	✔

This is not a complete list of side effects. For any unexpected effects while taking MIDODRINE, contact your doctor or pharmacist.

HOW TO STORE IT

Store away from heat and direct light. Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to : Canada Vigilance Program
    Health Canada
    Address Locator: 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, AA Pharma Inc. at:

1-866-469-1297

This leaflet was prepared by AA Pharma Inc.

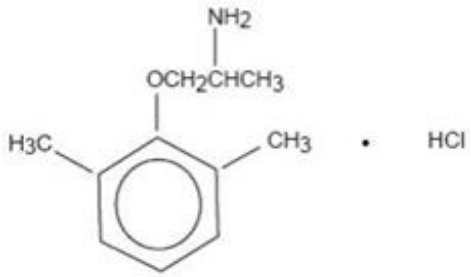
Last revised: May 26, 2010

MEXILETINE HYDROCHLORIDE- mexiletine hydrochloride capsule
Ingenus Pharmaceuticals, LLC

MEXILETINE HYDROCHLORIDE CAPSULES USP

DESCRIPTION

Mexiletine hydrochloride, USP is an orally active antiarrhythmic agent. It is a white to almost white powder, freely soluble in water and dehydrated alcohol. Mexiletine hydrochloride, USP has a pKa of 9.2. The chemical name of Mexiletine hydrochloride, USP is (±)1-methyl-2-(2, 6-xylyloxy) ethylamine hydrochloride and has the following structural formula is:



$C_{11}H_{17}NO•HCl$ M.W. 215.72

Each capsule for oral administration, contains 150 mg, 200 mg or 250 mg of mexiletine hydrochloride, USP. 100 mg of mexiletine hydrochloride is equivalent to 83.31 mg of mexiletine base. In addition each capsule contains the following excipients: pregelatinized starch, colloidal silicon dioxide, magnesium stearate. The capsule shell contains: gelatin, titanium dioxide, and FD&C Yellow #6. The 150 mg capsule also contains: FD&C Red #40 and FD&C Blue #1and the 250 mg capsule also contains: D&C Yellow #10 and FD&C Blue #1.

The imprinting ink contains: shellac, black iron oxide, N-butyl alcohol, isopropyl alcohol, propylene glycol, and ammonium hydroxide.

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 a prolonged QT interval.

In patients with preexisting 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 3 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 to12 hours. It is 50 to 60% bound to plasma protein, with a volume of distribution of 5 to 7 liters/kg. Mexiletine is mainly metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. With involvement of CYP2D6, there can be either poor or extensive metabolizer phenotypes. Since approximately 90% of mexiletine hydrochloride is metabolized in the liver into inactive metabolites, pathological changes in the liver can restrict hepatic clearance of mexiletine hydrochloride and its metabolites. The metabolic degradation proceeds via various pathways including aromatic and aliphatic hydroxylation, dealkylation, deamination and N-oxidation. Several of the resulting metabolites are submitted to further conjugation

with glucuronic acid (phase II metabolism); among these are the major metabolites p-hydroxymexiletine, hydroxy-methylmexiletine and N-hydroxy-mexiletine. 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, USP are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgment 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

BOXED WARNING

WARNINGS

Mortality

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

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

Acute Liver Injury

In postmarketing 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.

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.

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 of 475 in controlled clinical trials) with preexisting 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 preexisting 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 nonsustained 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-life of mexiletine, patients with liver disease should be followed carefully while receiving mexiletine. The same caution should be observed in patients with hepatic dysfunction secondary to congestive heart failure.

Concurrent drug therapy or dietary regimens which may markedly alter urinary pH should be avoided during mexiletine hydrochloride therapy. The minor fluctuations in urinary pH associated with normal diet do not affect the excretion of mexiletine.

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 of 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 a 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

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_C, 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.

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, 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 hydrochloride is deemed essential, an alternative method of infant feeding should be considered.

Pediatric Use

Safety and effectiveness in the pediatric patients 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 to1200 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. **Table 1** presents the adverse events reported in the one-month placebo-controlled trial.

Table 1: 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 Arrhythmia /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
Weakness	1.9	4.1
Fatigue	1.9	2
Tinnitus	1.9	4.1
Confusion/Clouded Sensorium	1.9	2
Other		
Headache	7.5	6.1
Blurred Vision/Visual Disturbances	7.5	2
Dyspnea/Respiratory	5.7	10.2
Rash	3.8	2
Non-specific Edema	3.8	-

Table 2 presents the adverse reactions occurring in one percent or more of patients in the three-month controlled studies.

Table 2: Comparative Incidence (%) of Adverse Events Among Patients Treated with Mexiletine or Control Drugs in the 12-Week Double-blind Trials

	Mexiletine N = 430	Quinidine N = 262	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/PVC's	1	2.7	2.6	-
Digestive				
Nausea/Vomiting/Heartburn	39.3	21.4	33.3	14.5
Diarrhea	5.2	33.2	2.6	8.7
Constipation	4	-	6.4	11.6
Changes in Appetite	2.6	1.9	-	-
Abdominal Pain/Cramps/Discomfort	1.2	1.5	-	1.4
Central Nervous System				
Dizziness/Lightheadedness	18.9	14.1	14.1	2.9
Tremor	13.2	2.3	3.8	1.4
Coordination Difficulties	9.7	1.1	1.3	-
Changes in Sleep Habits	7.1	2.7	11.5	8.7
Weakness	5	5.3	7.7	2.9
Nervousness	5	1.9	6.4	5.8
Fatigue	3.8	5.7	5.1	1.4
Speech Difficulties	2.6	0.4	-	-
Confusion/Clouded Sensorium	2.6	-	3.8	-
Paresthesias/Numbness	2.4	2.3	2.6	-
Tinnitus	2.4	1.5	-	-
Depression	2.4	1.1	1.3	1.4
Other				
Blurred Vision/Visual Disturbances	5.7	3.1	5.1	7.2
Headache	5.7	6.9	7.7	4.3
Rash	4.2	3.8	10.3	1.4
Dyspnea/ Respiratory	3.3	3.1	5.1	2.9
Dry Mouth	2.8	1.9	5.1	14.5
Arthralgia	1.7	2.3	5.1	1.4
Fever	1.2	3.1	2.6	-

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 treatment have been reported.

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.

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 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 infiltration and 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 drowsiness, nystagmus, ataxia, dyspepsia, hypersensitivity reaction, and exacerbation of congestive heart failure in patients with preexisting compromised ventricular function. There have been rare reports of pancreatitis associated with mexiletine treatment.

To report SUSPECTED ADVERSE REACTIONS, contact Ingenus Pharmaceuticals, LLC at 1-877-748-1970 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Clinical findings associated with mexiletine overdosage have included drowsiness, confusion, 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 4.4g with postmortem serum mexiletine level of 34 to 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 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**).

Loading Dose

When rapid control of ventricular arrhythmia is essential, an initial loading dose of 400 mg of mexiletine hydrochloride 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 hydrochloride 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: 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 to12 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, the lidocaine infusion should be stopped when the first oral dose of mexiletine hydrochloride 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 is supplied in bottles of 100 hard gelatin capsules containing 150 mg, 200 mg or 250 mg of mexiletine hydrochloride:

Mexiletine hydrochloride capsules USP, 150 mg capsules are Hard gelatin capsule with an opaque tan cap and an opaque orange body, imprinted with 'ING239' on both cap and body in black ink containing white to off-white granular powder. They are supplied in bottles of 100 capsules: NDC 50742-239-01.

Mexiletine hydrochloride capsules USP, 200 mg capsules are Hard gelatin capsule with an opaque orange cap and an opaque orange body, imprinted with 'ING240' on both cap and body in black ink containing white to off-white granular powder. They are supplied in bottles of 100 capsules: NDC 50742-240-01.

Mexiletine hydrochloride capsules USP, 250 mg capsules are Hard gelatin capsule with an opaque green cap and an opaque orange body, imprinted with 'ING241' on both cap and body in black ink containing white to off-white granular powder. They are supplied in bottles of 100 capsules: NDC 50742-241-01.

Store at 20°C to 25°C (68°C to 77°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required)

Rx Only

Manufactured for:

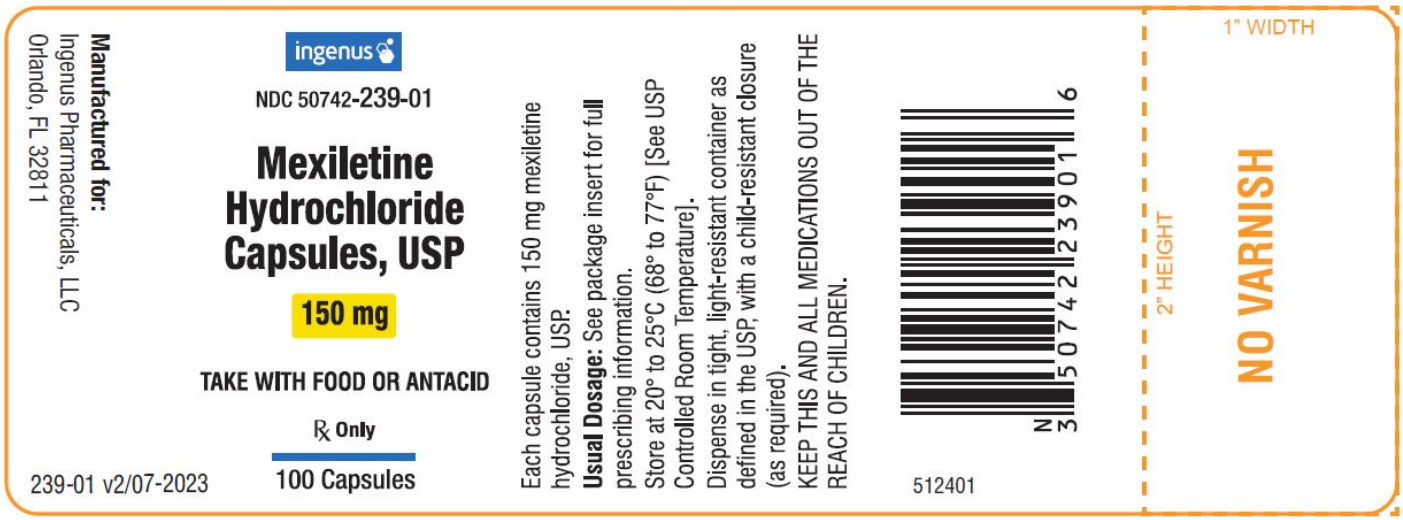
Ingenus Pharmaceuticals, LLC

Orlando, FL 32811

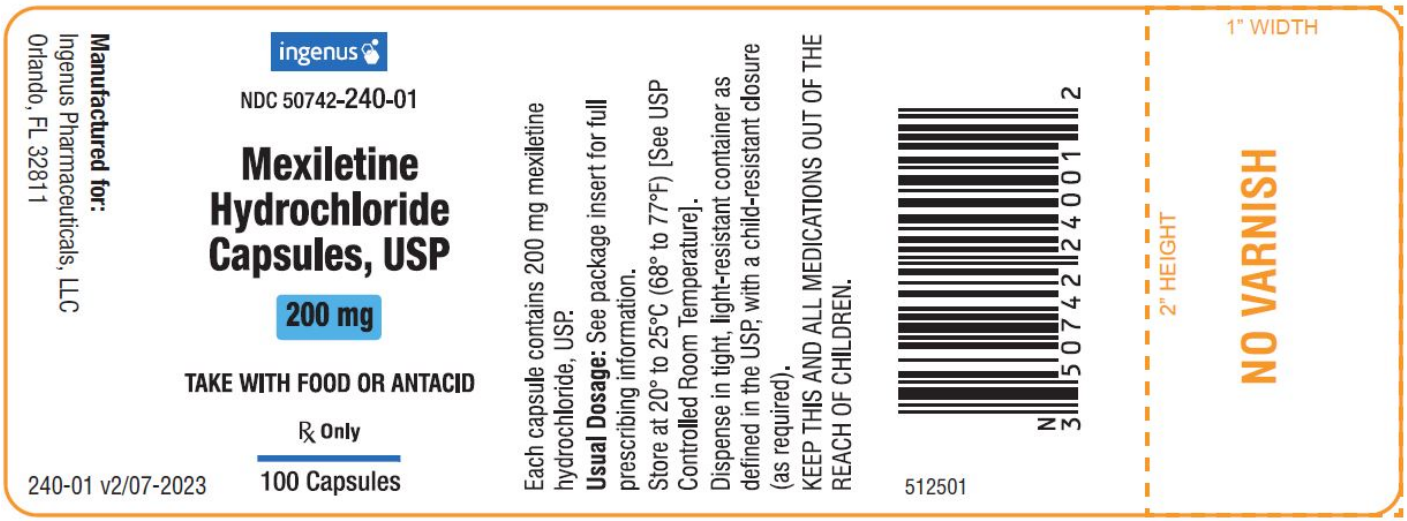
554601

Revised: 07/2023

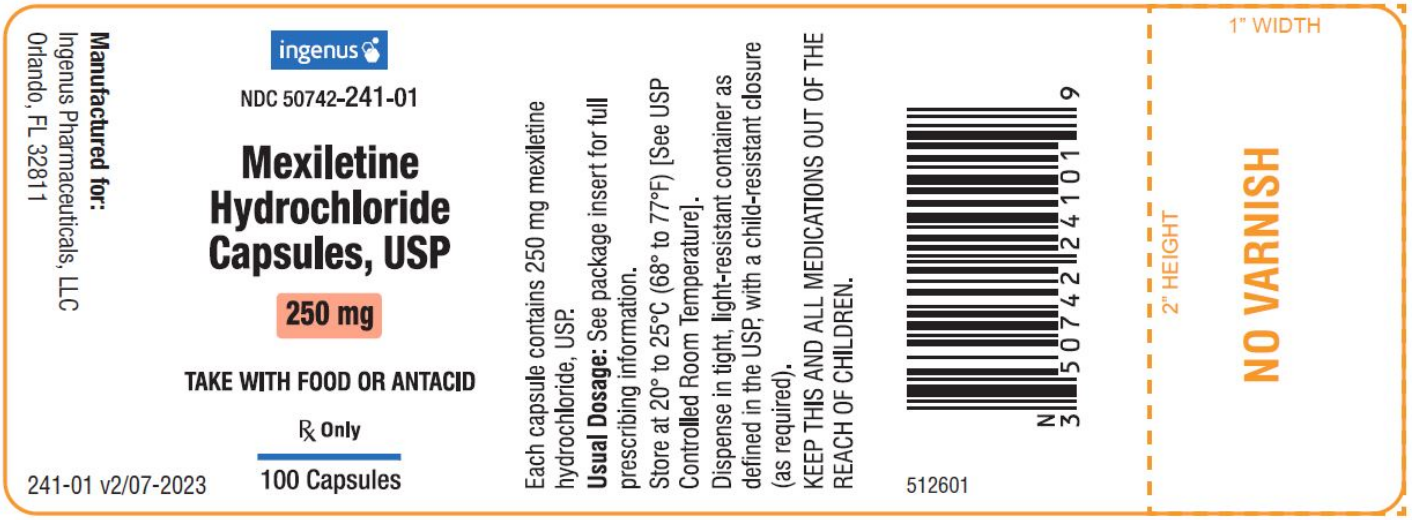
PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



Container Label - 150 mg



Container Label - 200 mg



Container Label - 250 mg

MEXILETINE HYDROCHLORIDE

mexiletine hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50742-239
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
MEXILETINE HYDROCHLORIDE (UNII: 606D60IS38) (MEXILETINE - UNII:1U511HHV4Z)	MEXILETINE HYDROCHLORIDE	150 mg

Inactive Ingredients	
Ingredient Name	**Strength**
STARCH, CORN (UNII: O8232NY3SJ)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
SHELLAC (UNII: 46N107B71O)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics			
Color	ORANGE (opaque tan cap and an opaque orange body)	**Score**	no score

Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	ING239
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50742-239-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	01/26/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA214352	01/26/2021	

MEXILETINE HYDROCHLORIDE

mexiletine hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50742-240
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEXILETINE HYDROCHLORIDE (UNII: 606D60IS38) (MEXILETINE - UNII:1U511HHV4Z)	MEXILETINE HYDROCHLORIDE	200 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
SHELLAC (UNII: 46N107B71O)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics

Color	ORANGE (opaque orange cap and an opaque orange body)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	ING240
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50742-240-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	01/26/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA214352	01/26/2021	

MEXILETINE HYDROCHLORIDE

mexiletine hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50742-241
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEXILETINE HYDROCHLORIDE (UNII: 606D60IS38) (MEXILETINE - UNII:1U511HHV4Z)	MEXILETINE HYDROCHLORIDE	250 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
SHELLAC (UNII: 46N107B71O)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics			
Color	GREEN (opaque green cap and an opaque orange body)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	ING241
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50742-241-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	01/26/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA214352	01/26/2021	

Labeler - Ingenus Pharmaceuticals, LLC (833250017)

Registrant - Novast Laboratories , Ltd. (527695995)

Establishment

Name	Address	ID/FEI	Business Operations
Ingenus Pharmaceuticals NJ, LLC		964680206	ANALYSIS(50742-239, 50742-240, 50742-241) , LABEL(50742-239, 50742-240, 50742-241) , MANUFACTURE(50742-239, 50742-240, 50742-241) , PACK(50742-239, 50742-240, 50742-241)

Revised: 7/2023 Ingenus Pharmaceuticals, LLC