PRODUCT MONOGRAPH

Pr RYTHMODAN®
Disopyramide capsules BP
100 mg

Antiarrhythmic Agent

ATC code: C01BA03

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1 THERAPEUTIC CLASSIFICATION

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2 ACTION AND CLINICAL PHARMACOLOGY

In both animal and man the electrophysiological and hemodynamic effects of RYTHMODAN® (disopyramide) are qualitatively similar to those of quinidine and procainamide.

Although the exact mechanism of action has not been completely elucidated, it would appear from animal studies that RYTHMODAN® exerts its antiarrhythmic activity in the following manner:

1. Reduces automaticity in cardiac Purkinje fibres by depressing the slope of phase 4 diastolic depolarization. The action manifests itself both in normal Purkinje fibres and in fibres damaged by either ischemia or infarction.

2. Depresses conduction velocity in atria, A-V node, Purkinje fibres, and ventricular muscle by decreasing the rate of rise of phase 0 depolarization in these fibres.

3. Prolongs action potential duration and effective refractory period in atria, Purkinje fibres and ventricular muscle.

4. Depresses excitability of both atrial and ventricular muscles by its direct effect on the myocardium.

5. Although the anticholinergic action of RYTHMODAN® may cause an increase in the sinus rate of normal hearts the usual effect on the rapid cardiac rate associated with an arrhythmia is a decrease, with possibly a reduction in blood pressure. RYTHMODAN® exerts a negative inotropic action on cardiac muscle.

RYTHMODAN® is rapidly absorbed after oral administration and reaches peak levels in about 1 to 2 hours. Absorption is slower with the long acting form, peak levels being reached in 4.5 to 6.2 hours.

Serum levels of disopyramide are correlated with antiarrhythmic activity. Usual therapeutic plasma levels are 2-4 mcg/mL. At these concentrations, disopyramide in the blood is about equally distributed between plasma and erythrocytes. Plasma protein binding of disopyramide in

humans varies with drug concentration. At therapeutic concentrations, protein binding is about 50%. Toxic plasma levels have not been defined in man, but are thought to exceed 10.5 mcg/mL.

Mean plasma half-life of disopyramide in healthy humans is 6.7 hours (range of 4-10 hours) while with the long acting form it is 14.5 hours, and even longer in ill, hospitalized patients. Patients with impaired renal function (creatinine clearance less than 40 mL/minute) have demonstrated disopyramide half-lives of 10-18 hours. Hepatic impairment may also prolong the half-life. Little or no tissue accumulation occurs.

In healthy humans, urinary and fecal excretion of disopyramide and its metabolites account for about 80% and 10% of the dose, respectively. Forty percent (40%) to 60% of a given dose is excreted in the urine as the unchanged drug and 15% - 25% as the mono-N-dealkylated metabolite. The remainder of a given dose is excreted via the bile into the feces. The plasma concentration of this metabolite is about 1/10th that of disopyramide.

3 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.

RYTHMODAN® (disopyramide) is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia. RYTHMODAN® 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 RYTHMODAN® 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, RYTHMODAN® 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.

The effects of RYTHMODAN® in patients with recent myocardial infarction have not been adequately studied and, therefore, its use in this condition cannot be recommended.

4 CONTRAINDICATIONS

RYTHMODAN® (disopyramide) is contraindicated in the presence of shock, renal failure, severe intraventricular conduction defects (i.e. bundle-branch block associated with first-degree atrioventricular block, double block [left posterior or anterior hemiblock and right bundle-branch

block]), pre-existing second and third degree A-V block (if no pacemaker is present), known hypersensitivity to the drug or to any ingredient in the formulation (for a complete list, see AVAILABILITY OF DOSAGE FORMS).

RYTHMODAN® is contraindicated in patients with a pre-existing long QT (see WARNINGS - OTHER CARDIAC EFFECTS, Q-T Prolongation).

RYTHMODAN® is contraindicated in patients with severe sinus node dysfunction (see PRECAUTIONS - PATIENTS WITH SPECIAL DISEASE OR CONDITIONS, Conductions Abnormalities).

RYTHMODAN® should not be used in the presence of uncompensated or inadequately compensated congestive heart failure (see WARNINGS).

RYTHMODAN® is contraindicated in most patients with extensive myocardial disease, but may on occasion be used in these patients under the close supervision of a cardiologist if in their opinion the patient's condition justifies it. When used in these patients continuous ECG monitoring in a CCU facility is mandatory.

Due to its anticholinergic activity, RYTHMODAN® is contraindicated in patients with glaucoma or in patients in whom urinary retention is present (see PRECAUTIONS).

Concomitant administration of RYTHMODAN® with other antiarrhythmics or other drugs liable to provoke ventricular arrhythmias and especially torsade de pointes is contraindicated (see PRECAUTIONS - DRUG INTERACTIONS, Concomitant Antiarrhythmic Therapy and Drugs Associated with Risk of «torsade de pointes»).

5 WARNINGS

- GENERAL

All antiarrhythmic drugs can produce unwanted effects when they are used to treat symptomatic but not life threatening arrhythmia; the expected benefit should be balanced against their risks.

Proarrhythmia and cardiac decompensation are special risks associated with the use of antiarrhythmic drugs in patients with structural heart disease. Special caution should be exercised when prescribing in this context (see PRECAUTIONS - DRUG INTERACTIONS, Concomitant Antiarrhythmic Therapy).

Life threatening and hemodynamically significant arrhythmia are difficult to treat and affected patients are at high risk. Treatment of these arrhythmias, whatever modality, must be initiated in the hospital.

- 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.

- NEGATIVE INOTROPIC PROPERTIES

Heart Failure

Because of its negative inotropic effect disopyramide may cause or worsen congestive heart failure. Therefore, this drug should not be used in patients with heart failure, and should be especially avoided in patients with a previous history of heart failure except in the very special circumstances described below:

In patients in whom the failure is exacerbated or caused by an arrhythmia, RYTHMODAN® may be used to suppress the ectopy but it must be borne in mind that any such benefit on cardiac function may be overcome by the depressant effect on cardiac output, and thereby result in even worse failure even though routine methods of anti-failure therapy including optimal digitalization are attempted. Careful monitoring is essential under these circumstances.

Patients with compensated heart failure may be treated with RYTHMODAN®, but careful attention must be given to the maintenance of cardiac function including optimal digitalization. Close observation is mandatory, as any benefit of RYTHMODAN® either therapeutic or prophylactic could be accompanied by an unacceptable lowering of cardiac output.

For most patients the encroachment on their cardiac reserve may be of minimal clinical consequence, but in patients with a limited reserve as a result of pump dysfunction and/or imbalanced work load, even a minor encroachment on reserve can precipitate clinically evident failure or make its control more difficult, and even result in a gross low output congestive cardiac failure state.

Hypotension

On rare occasions RYTHMODAN® has caused syncope with sudden loss of consciousness. In the cases reported, this was believed to be due to an excessive hypotensive action of the drug or, in some cases, due to concomitant use with other hypotensive or negative inotropic agents.

Severe hypotension following RYTHMODAN® administration has been observed usually in patients with primary myocardial disease (cardiomyopathy), and also in inadequately compensated congestive heart failure or advanced myocardial disease with low output state, or in patients on other hypotensive medication e.g., beta-adrenergic blockers or verapamil. An oral

loading dose of RYTHMODAN® should not be given to such patients; initial dosage and subsequent dosage adjustments should be made under close supervision.

If severe hypotension develops, RYTHMODAN® should be discontinued promptly (see DRUG INTERACTIONS).

- OTHER CARDIAC EFFECTS

QRS Widening

Significant widening (greater than 25%) of the QRS complex may occur during RYTHMODAN® administration; in such cases RYTHMODAN® should be discontinued.

Q-T Prolongation

As with other quinidine-like antiarrhythmic drugs, prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur with RYTHMODAN®, particularly in response to higher doses. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If a Q-T prolongation greater than 25% is observed and if ectopy continues, the patient should be monitored closely, and consideration be given to discontinuing RYTHMODAN®.

Disopyramide, as with other quinidine-like antiarrhythmic drugs, has been associated with torsade de pointes.

Heart Block

If first-degree heart block develops in a patient receiving RYTHMODAN®, the dosage should be reduced. If the block persists despite reduction of dosage, continuation of the drug must depend upon weighing the benefit being obtained against the risk of higher degree of heart block. Development of second or third degree A-V block or unifascicular or trifascicular block requires discontinuation of RYTHMODAN® therapy, unless the ventricular rate is adequately controlled by a temporary or implanted ventricular pacemaker (see CONTRAINDICATIONS).

Anticholinergic Activity

Glaucoma

Disopyramide phosphate should be avoided in patients with glaucoma (see CONTRAINDICATIONS). In patients with a history or family history of glaucoma, intraocular pressure should be measured before initiating treatment.

6 PRECAUTIONS

- PATIENTS WITH SPECIAL DISEASES OR CONDITIONS

Atrial Tachyarrhythmias

RYTHMODAN® is usually ineffective in atrial flutter and its usefulness in atrial fibrillation is not proven. If atrial flutter or fibrillation is present, the patient should be fully digitalized prior to RYTHMODAN® use so that drug-induced changes in A-V conduction do not result in an increase of ventricular rate beyond physiologically acceptable limits.

Conduction Abnormalities

RYTHMODAN® therapy in patients with sick sinus syndrome (including bradycardia-tachycardia syndrome), Wolff-Parkinson White (WPW) syndrome or bundle branch block requires care, since the effect of RYTHMODAN® in these conditions is difficult to predict. Sinoatrial node function deterioration has been reported in sick sinus syndrome patients treated with disopyramide (see CONTRAINDICATIONS).

Digitalis Intoxication

Since RYTHMODAN® has not been studied in patients with digitalis intoxication, it should be used with caution in these patients.

Urinary retention
Urinary retention may occur in patients of either sex, but males with benign prostatic hypertrophy are at particular risk. If acute urinary retention develops, RYTHMODAN® therapy should be temporarily discontinued, except in occasional instances, in which continued control of the arrhythmia with RYTHMODAN® is considered mandatory. In such cases, overriding measures should be taken (e.g., catheter drainage or operative relief). If RYTHMODAN® is discontinued, and later reintroduced, a lower dose should be used (see CONTRAINDICATIONS).

Paralytic ileus
There is a risk of paralytic ileus, especially in the elderly, in a context of concomitant use with anticholinergic drugs or increased plasma levels of disopyramide (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Myasthenia gravis
RYTHMODAN® should be used with special care in myasthenia gravis since its anticholinergic properties could precipitate a myasthenic crisis.

Elderly patients
Available data suggest that the use of drugs with anticholinergic properties in elderly patients may lead to cognitive disorders during the course of treatment.

Renal Impairment

More than 50% of disopyramide is excreted unchanged in urine. Therefore, in impaired renal function reduce the dose and increase the dosing interval (see DOSAGE AND ADMINISTRATION); ECG should be carefully monitored for prolongation of PR interval, QRS widening, or other signs of overdosage (see ACTION AND CLINICAL PHARMACOLOGY and SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Hepatic Impairment

Hepatic impairment also increases disopyramide plasma half-life; reduce dosage for patients with such impairment. The ECG should be carefully monitored for signs of overdosage.

Hypokalemia

Although there is no experience with RYTHMODAN® in severe hypokalemia, other antiarrhythmic agents are frequently ineffective or may be hazardous in such patients, as potassium abnormalities can by themselves induce arrhythmia; a significant potassium deficit should be corrected before instituting RYTHMODAN® therapy**.**

Patients having concomitant treatment with diuretics, stimulant laxatives or other hypokalemia inducing drugs are at particular risk of hypokalemia (see PRECAUTIONS - DRUG INTERACTIONS, Hypokalemia inducing drugs).

During treatment with disopyramide, potassium imbalance should be checked and corrected if necessary.

Hypoglycemia

Significant lowering of blood glucose, sometimes severe, associated with the risk of occurrence of consciousness disorder including hypoglycemic coma, has occasionally been reported during disopyramide administration. The physician should be alert to this possibility, especially in patients with congestive heart failure, the elderly, treated diabetics, chronic malnutrition, hepatic, renal or other diseases, or who are taking drugs (e.g. beta-adrenergic blockers, alcohol) which could compromise preservation of the normal gluco-regulatory mechanisms in the absence of food.

In these patients blood glucose levels should be carefully monitored (see DRUG INTERACTIONS).

Pregnancy

Animal studies have not demonstrated any teratogenic effect and only minimal evidence of impaired fertility.

Disopyramide has been reported to stimulate contraction of the pregnant uterus.

RYTHMODAN® (disopyramide) should be used in pregnant women only when it is clearly indicated and the benefit/risk ratio has been carefully evaluated.

Lactation

Disopyramide is excreted in human milk. Therefore, if use of the drug is deemed essential in lactating women, an alternative method of infant feeding should be instituted.

Children

The safety and effectiveness of RYTHMODAN® in children have not been established and are therefore not recommended in this population.

- DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

Some adverse reactions may impair the patient's ability to concentrate and react, and hence the ability to drive or operate machinery (see ADVERSE REACTIONS).

- DRUG INTERACTIONS

Concomitant Antiarrhythmic Therapy

The concomitant use of RYTHMODAN® with other *Class I antiarrhythmic agent and/or beta - adrenergic blockers* should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. This should be considered particularly in patients with any degree of cardiac decompensation or those with a prior history, thereof. Patients receiving more than one antiarrhythmic drug must be carefully monitored.

Proarrhythmia and cardiac decompensation are special risks associated with the use of antiarrhythmic drugs in patients with structural heart disease. Special caution should be exercised when prescribing in this context (see WARNINGS - GENERAL).

Administer RYTHMODAN® cautiously to patients who have recently received other antiarrhythmic drugs. RYTHMODAN® should not be started until at least one half-life after stopping the other antiarrhythmic agent (Half-life of quinidine is about 6 hours. Half-life of procainamide is about 3 hours). In these cases loading dose of RYTHMODAN® should not be used. Excessive widening of QRS or excessive negative inotropic effect may occur.

Combinations of antiarrhythmic drugs are not well researched and their effect may be unpredictable. Thus, antiarrhythmic combination should be avoided.

Quinidine
Concomitant administration of disopyramide and quinidine resulted in slight increases in plasma disopyramide levels and slight decreases in plasma quinidine levels.

Verapamil
Although the interaction is poorly documented, the concurrent use of verapamil and disopyramide may aggravate or precipitate congestive heart failure or result in excessive hypotension (see WARNINGS).

Digoxin
Concomitant digoxin and disopyramide therapy has not resulted in changes in serum digoxin levels.

Drugs Associated with Risk of "torsade de pointes"

Combination with drugs associated with risk of "torsade de pointes" is not recommended (see WARNINGS - OTHER CARDIAC EFFECTS, Q- T Prolongation)

Anticholinergic Agents

The anticholinergic effect of disopyramide may be additive with that of other agents having anticholinergic properties (i.e. atropine).

Phosphodiesterase Type 5 Inhibitors

There is evidence that phosphodiesterase Type 5 inhibitors may be potentially associated with a risk of QT prolongation. Concomitant administration of disopyramide with such drugs may potentially enhance this QT prolongation effect and is not recommended.

Drugs Affecting Hepatic Microsomal Enzymes

There is some evidence that disopyramide is metabolized by hepatic CYP3A.

Although human studies are not available, concomitant administration of significant inhibitors of this enzyme (e.g. certain macrolide, azole antifungal antibiotics) may increase the serum levels of disopyramide.

Drugs (e.g.: *phenobarbital, rifampin, phenytoin*) that induce hepatic microsomal enzymes may accelerate the metabolism of disopyramide, resulting in lower plasma concentrations. When microsomal enzymes inducers are used concomitantly with disopyramide, serum concentrations of disopyramide should be closely monitored to avoid subtherapeutic concentrations.

When prescribing a drug metabolized by CYP3A (such as theophylline, H.I.V. protease inhibitors [e.g. ritonavir, indinavir, saquinavir], cyclosporin A, warfarin), it should be kept in mind that disopyramide is probably also a substrate of this isoenzyme and thus competitive inhibition of metabolism might occur, possibly increasing serum levels of these drugs.

Since the magnitude of potential effects is not foreseeable, combinations of disopyramide with inducers or inhibitors of CYP3A4 are not recommended.

Erythromycin

There are reported cases of patients with clinically stable cardiac condition under disopyramide therapy where the addition of erythromycin resulted in polymorphic ventricular tachycardia, QTc prolongation, and elevation of disopyramide serum levels. Erythromycin appears to inhibit disopyramide metabolism in the liver. Additional documentation is needed to substantiate this possible interaction. However closer monitoring is advised when the two drugs are combined.

Ethanol

In healthy subjects, ethanol did not affect the half-life or total body clearance of disopyramide. However, combination could result in hypoglycemia in patients at risk (see PRECAUTIONS - Hypoglycemia).

Insulin

There have been reports of potentiation of the hypoglycemic effect of insulin by disopyramide (see PRECAUTIONS - Hypoglycemia).

Warfarin

Potentiation of the hypoprothrombinemic effect of warfarin has been reported in several patients receiving disopyramide and warfarin. However, in a study in several patients receiving disopyramide and warfarin concomitantly, the hypoprothrombinemic effect of warfarin was not increased and, in 2 patients, actually was decreased slightly. Further study is needed to determine whether a potential interaction exists.

Hypokalemia Inducing Drugs

The concomitant use of stimulant laxatives is not recommended, as patients are at particular risk of hypokalemia**.** The use of another type of laxative is more appropriate (see PRECAUTIONS - PATIENTS WITH SPECIAL DISEASES OR CONDITIONS, Hypokalemia).

Precaution should also be exercised in case of association with other hypokalemia inducing drugs, such as: potassium-depleting diuretics (e.g. thiazides, furosemide, ethacrinic acid), amphotericin B, cosyntropin (corticotrophin analogue), gluco and mineralo-corticoids (see PRECAUTIONS - PATIENTS WITH SPECIAL DISEASES OR CONDITIONS, Hypokalemia).

7 ADVERSE REACTIONS

Rare occurrence of congestive heart failure (CHF), hypotension, widening QRS, sinus arrest, nodal rhythm dissociation, cardiac arrest and cardiovascular collapse have been reported. An occasional paradoxical ventricular tachycardia, evolving sometimes to fibrillation has been observed. A definite relationship to the drug was not always established in the above cardiovascular effects.

Intra-cardiac conduction abnormalities may occur: QT interval prolongation, atrioventricular block and bundle-branch block**.**

Other types of arrhythmia have been reported: bradycardia, sinus block.

The most common adverse reactions which are dose dependent are associated with the anticholinergic properties of the drug. These may be transitory, but may be persistent and can be severe. Urinary retention is the most serious anticholinergic effect.

The following reactions were reported in more than 10% of patients:

Anticholinergic: dry mouth (16-30%), urinary retention (7-13%), constipation.

Gastrointestinal: nausea, indigestion, vomiting, diarrhea, flatulence, bad taste in the mouth, anorexia.

The following reactions were reported in 1 to 10% of patients:

Anticholinergic: blurred vision, dry eyes/nose/throat.

Cardiovascular: hypotension with or without CHF, increased CHF, cardiac conduction disturbances, proarrhythmic effects (6%), œdema, dyspnea, cyanosis, chest pain.

Dermatologic: skin reactions including pruritus, urticaria, morbilliform eruption, abdominal rash, photosensitization.

General: dizziness, vertigo, drowsiness, profuse sweating.

Genitourinary: urinary hesitancy and frequency.

Other: raised SGOT levels.

The following were reported in less than 1% of patients: dysuria, headache, feeling of warmth, pallor, peripheral paresthesia, fatigue, malaise, insomnia, confusion, transitory psychosis, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, hypoglycemia (sometimes severe, associated with the risk of occurrence of consciousness disorder including hypoglycemic coma), neutropenia, idiosyncratic reaction to drug. In a few instances cholestatic jaundice has been reported. A definite causal relationship has not been established.

A high plasma concentration has been associated with impotence.
Other atropine-like ocular adverse reactions were reported: disorders of accommodation, diplopia.

Other atropine-like effects were reported: cognitive disorders, psychiatric disorders.

Epigastralgia has been also reported.

Skin reactions: very rarely, rashes; isolated reports of anaphylactic-type reactions (e.g. angioedema) possibly culminating in shock (essentially reported in association with the injectable formulation).

Post-Market Adverse Drug Reactions

Blood and lymphatic system disorders
Agranulocytosis

8 SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Patients who took deliberate overdoses of oral disopyramide presented with an early loss of consciousness after an apneic period, cardiac arrhythmias and loss of spontaneous respiration, leading to death. Serum levels in these patients were as high as 114 mg/L taken at various times after ingestion, including post-mortem.

The clinical signs of overdose may also include: paralytic ileus, bilateral mydriasis (suggestive of overdose); syncope, hypotension or shock; cardiac arrest due to intraventricular block or asystole; respiratory symptoms; coma (with bilateral mydriasis) in cases of massive intoxication.

Toxic plasma levels of disopyramide produce excessive widening of QRS complex and QT interval as a premonitory sign of other arrhythmias, in particular torsade de pointes which can result in repeated syncopes, worsening of CHF, hypotension, varying kinds and degrees of conduction disturbance, bradycardia and finally asystole. Obvious anticholinergic effects are also observed.

Treatment

Discontinue drug and initiate gastric lavage; no specific antidote has been identified; treatment of overdosage should be symptomatic and may include the administration of isoproterenol, dopamine, intra-aortic balloon counterpulsation, mechanically assisted respiration and hemoperfusion with charcoal.

Hemodialysis may be employed to rapidly lower serum concentration of drug. In vitro studies with human blood have demonstrated good dialyzability. Its clearance was 33 mL/minute at a blood flow of 250 mL/ minute when an initial plasma concentration of 22 mcg/mL was dialysed using an artificial kidney (Cordis-DOW-4).

The ECG should be monitored and supportive therapy with vasopressors, sympathomimetics, cardiac glycosides and diuretics should be given, as required.

Should progressive heart block develop, endocardial pacing should be implemented. In case of any impaired renal function, measures to increase glomerular filtration rate may reduce the toxicity (disopyramide is excreted primarily by the kidney). Altering the urinary pH in man does not affect plasma half-life or the amount of disopyramide excreted in urine.

The anticholinergic effects could be reversed with neostigmine, at the discretion of the physician.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

9 DOSAGE AND ADMINISTRATION

The dosage of RYTHMODAN® should be individualized for each patient, based upon response and tolerance and patient weight.

Capsules

The usual daily dose of RYTHMODAN® is 400-800 mg given in 4 divided doses. Rarely, control may be maintained on daily doses of less than 400 mg.

If rapid control of arrhythmia is essential, an initial dosage schedule for most adults is a single loading dose of 300 mg followed by 100 mg every 6 hours. If satisfactory control of the arrhythmias not obtained with the maintenance dose of 100 mg q 6 hours, increase to 150 mg or subsequently to 200 mg q 6 hours if necessary.

For patients with cardiomyopathy or possible cardiac decompensation, loading doses should not be given, an initial dosage should be limited to 100 mg of RYTHMODAN® every 6 hours. Subsequent dosage adjustments should be made gradually with close monitoring for possible development of hypotension and/ or congestive heart failure (see WARNINGS).

For patients of small stature (body weight less than 50 kg or 110 lbs) and for patients with mild hepatic or renal insufficiency (creatinine clearance above 60 mL/minute), a loading dose of 200 mg is recommended, followed by 100 mg every 6 hours. The recommended maintenance dose of these patients is 400 mg per day given in doses of 100 mg every 6 hours.

In patients with severe hepatic or renal insufficiency (creatinine clearance below 50 mL/minute), an initial loading dose of 100 mg is recommended. These patients are best managed with repeated plasma disopyramide determinations and subsequent dosage and frequency of administration should be based on the results of these determinations (see PRECAUTIONS).

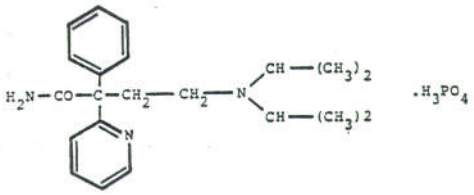
RYTHMODAN® Capsules Dosage Interval for Patients With Renal Insufficiency			
Creatinine clearance (mL/minute)	40 - 30	30 - 15	<15
Approximate maintenance-dosing interval	q 8 h	q 12 h	q 24 h

No loading dose should be given to patients who are being transferred from other oral antiarrhythmic agents such as quinidine or procainamide (see PRECAUTIONS - DRUG INTERACTIONS).

10 PHARMACEUTICAL INFORMATION

(disopyramide)

Chemical Structure:



Molecular Formula: $C_{21}H_{29}N_3O$ Molecular Weight (base): 339.5

Molecular Formula: $C_{21}H_{29}N_3O.H_3PO_4$ Molecular Weight (phosphate): 437.5

Chemical Name: 4-diisopropylamino-2-phenyl-2-(2-pyridyl) butyramide.

Description: Disopyramide is a stable white powder, insoluble in water but soluble in dilute acid or organic solvents.

Disopyramide phosphate is a stable white powder with a molecular weight of 437.5.

It is soluble in water.

11 AVAILABILITY OF DOSAGE FORMS

RYTHMODAN® 100 mg capsules are presented in green/yellow, hard gelatin capsules marked RY RL. Each capsule contains 100 mg disopyramide. The capsules are available in blister packs of 84 (6 x 14).

Non-medicinal ingredients: Corn starch, magnesium stearate, pregelatinized starch, talc. *Capsule Body and Head*: FD&C Blue #2, gelatin, titanium dioxide, yellow iron oxide.

12 PHARMACOLOGY

Antiarrhythmic Activity in Animals

Activity against slow unifocal and rapid multifocal ventricular arrhythmias induced by experimental myocardial infarction (at i.v. doses of 1 to 3 mg/kg and 5 mg/kg, respectively) against ouabain or epinephrine induced ventricular arrhythmias (at doses of 5 to 10 mg/kg i.v.) in anesthetized dogs.

A weak, negative inotropic effect on isolated heart preparations and a reduction in the contractile force of the heart *in situ*. A decrease in cardiac output (which was not prevented by pre-treatment with cardiac glycosides) was seen in the anesthetized, open-chest, beagle at a dose of 3 mg/kg i.v.

Local anesthetic activity approximately equivalent to lignocaine but of longer duration in guinea-pig (wheal) and mouse (nerve conduction) tests.

Electrophysiology

A decrease in conduction velocity through the atria, A-V node and His-Purkinje system was seen in dog heart *in situ*. Isolated preparations revealed an increase in the duration of the action potential, accompanied by a decreased amplitude and rate of rise of the phase 0 of the action potential. Membrane responsiveness was decreased and the effective refractory period increased with consequent increased diastolic thresholds and reduced cardiac excitability.

In man disopyramide prolongs the effective refractory period of the atria and the ventricles. The effective refractory period of the A-V node is either slightly shortened or unchanged. The relative refractory period of the His-Purkinje system is prolonged. A-V nodal conduction time is unchanged by disopyramide. Conduction through the His-Purkinje system is unchanged, or slightly delayed.

Hemodynamics

The main hemodynamic changes induced in patients by disopyramide are:

1. Heart rate unchanged or slightly increased.
2. Cardiac output unchanged or lowered by 10-25%.
3. Peripheral resistance increased or unchanged.
4. Effects on blood pressure were inconsistent but usually there was a slight fall.
5. Left ventricular end diastolic pressure unchanged or increased.
6. Negative inotropic effect which can be marked in patients with depressed left ventricular function.

Pharmacokinetics of RYTHMODAN®-LA

After a single oral dose of 250 mg long acting disopyramide to healthy volunteers, a mean peak plasma concentration of 1.86 mcg/mL was reached in approximately 4.5 hours with an elimination half-life of 14.5 hours. Steady state was achieved after 4 days of dosing.

In hospitalized patients after a single oral dose, the mean plasma concentration was 2.84 mcg/mL with a time to peak of 6.2 hours. The half-life was shown to be longer in hospitalized patients.

There was no evidence of accumulation following oral treatment with 250 mg bid of long-acting disopyramide for 30 days in patients previously taking 2 x 100 mg tid of regular disopyramide.

Metabolism

In man, disopyramide is metabolized by N-dealkylation. After an oral dose of approximately 6 mg/kg disopyramide phosphate to normal healthy volunteers, about 80% of the administered dose was recovered in the urine and 15% in the feces. Of these amounts 29% in the urine and 64% in the feces were present as the mono-N-dealkylated metabolite. This suggests at least 90% absorption of the orally administered drug, and a significant biliary excretion. In the plasma 80% was unchanged drug and 7% was the monodealkylated metabolite.

Both disopyramide and, to a lesser extent, its monodealkylated metabolite, bind to plasma proteins, the extent of binding being dependent upon plasma concentration.

13 TOXICOLOGY

- ACUTE

Oral

The LD_{50} in mice of disopyramide base is 480 ± 97 mg/kg. Dyspnea and convulsions occurred at doses of 250 mg/kg and above. The LD_{50} of RYTHMODAN®-LA 250 mg tablets determined in rats and mice were:

Combined Males/Females:
Rats: 1010 mg/kg (894.5 - 1140.4 mg/kg)
Mice: 800 mg/kg (684 - 936 mg/kg)

Intravenous

The LD_{50} in mice of disopyramide base is 60 ± 5.5 mg/kg and of disopyramide phosphate is 70.8 mg/kg. Dyspnea and convulsions occurred at doses of 50 mg/kg and above.

The LD_{50}'s determined in rats were:
Male: 133 mg/kg (113 to 157 mg/kg)
Female: 148 mg/kg (126 to 173 mg/kg)

The minimal lethal dose in dogs infused with disopyramide at 6 mg/kg/minute was 35-50 mg/kg. Terminal signs were gasping, bulging eyes, cyanosis and apnea; death was believed to be due to myocardial failure.

- SUBACUTE

Intravenous doses of 7.5, 15 and 30 mg/kg were administered once daily to dogs for 3 weeks. There were no deaths and no significant findings at autopsy. Retching, vomiting, salivation and tremors of a transient nature were noted in most dogs in the 15 and 30 mg/kg dose groups.

Rats were treated with daily intravenous doses of 12, 30 and 75 mg/kg for three weeks. No compound effect was evident at the 12 and 30 mg/kg dosage levels. At the 75 mg/kg level, administration of the first dose resulted in immediate death of three rats. The survivors exhibited pallor, rapid respiration, increased heart beat and poor coordination. Three more deaths occurred after reducing the dosage to 60 mg/kg. Autopsy of the animals that died or were sacrificed at termination revealed no significant effects.

- CHRONIC

Oral doses of 100, 200 or 400 mg/kg were given to rats daily for 40 weeks and for 78 weeks. Dose related growth suppression, with corresponding decrease in organ weights, was observed in all three test groups.

Studies of 26 weeks and 52 weeks duration were conducted in dogs. Daily disopyramide doses of 30, 75 and 120 mg/kg in the 26 week study, and 30, 75 and 100 mg/kg in the 52 week study, were given in 3 divided doses.

A dose of 120 mg/kg/day was lethal to 4 (3 male and 1 female) out of 10 dogs studied. Shortly before death the dogs were observed to develop generalized muscular weakness. Electrocardiograms indicated myocardial depression. At autopsy, signs of passive congestion in the heart and liver were observed in 2 dogs, probably resulting from circulatory failure. A mild treatment-related hypokalemia was seen in male dogs in the 52 week study.

- MUTAGENICITY

Mutagenicity studies using the micronucleus test in mice, the diffusion test in E. coli and Ames Test were negative.

- TERATOLOGY

Oral

No evidence of teratogenicity was observed when disopyramide was fed to pregnant rats (days 1-21 of gestation) in doses of 50 and 150 mg/kg. The higher dose caused an increase in the number of small fœtuses (57%, compared to 19% in controls).

In rabbits fed 30 and 60 mg/kg on days 7-22 of gestation the lower dose had no significant effect. The 60 mg/kg dose produced 28% resorptions (compared to 7% in controls) but no teratogenic effect.

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