

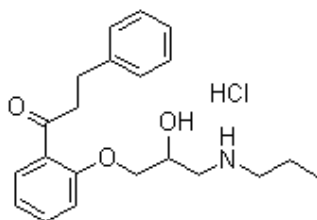
Data Sheet

RYTMONORM® 150mg
RYTMONORM® 300mg

Name of the Medicine

Propafenone hydrochloride tablets

Chemical Structure



CAS Number

34183-22-7

Description

Is a white or colourless crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol. Its chemical name is 2'-[2-hydroxy-3-(propylamino)-propoxy]-3-phenylpropiophenone hydrochloride and its chemical formula is C₂₁H₂₇NO₃.HCl. Its molecular weight is 377.92.

Pharmacology

Pharmacodynamics

Actions

Rytmonorm (propafenone HCl) is a Class Ic antiarrhythmic drug with local anaesthetic effects, and a direct stabilising action on myocardial membranes. The electrophysiological effect of Rytmonorm manifests itself in a reduction of up-stroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fibers, Rytmonorm reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity. Studies in anaesthetised dogs and isolated organ preparations show that Rytmonorm has beta-sympatholytic activity at about 1/50 of potency of propranolol. Clinical studies employing isoproterenol challenge and exercise testing after single doses of propafenone indicate a beta-adrenergic blocking potency (per mg) about 1/40 that of propranolol in man. In clinical trials, resting heart rate decreases of about 8% were noted at the higher end of the therapeutic plasma concentration range. At very high concentrations in vitro, propafenone can inhibit the slow inward current carried by calcium but this calcium antagonist effect probably does not contribute to antiarrhythmic efficacy. Propafenone has local anaesthetic activity approximately equal to procaine.

Electrophysiology:

Electrophysiology studies in patients with ventricular tachycardia have shown that Rytmonorm prolongs atrioventricular (AV) conduction while having little or no effect on sinus node function. Both AV nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged. Propafenone has little or no effect on the atrial functional refractory period, but AV nodal functional and effective refractory periods are prolonged. In patients with Wolff-Parkinson-White (WPW), Rytmonorm reduces conduction and increases the effective refractory period of the accessory pathway in both directions. Propafenone slows conduction and consequently produces dose-related changes in the PR interval and QRS duration. QT_c interval does not change.

(See table below)

Mean Changes in ECG Intervals*								
Total Daily Dose (mg)								
	337.5mg		450mg		675mg		900mg	
Interval	msec	(%)	msec	(%)	msec	(%)	msec	(%)
RR	-14.5	-1.8	30.6	3.8	31.5	3.9	41.7	5.1
PR	3.6	2.1	19.1	11.6	28.9	17.8	35.6	21.9
QRS	5.6	6.4	5.5	6.1	7.7	8.4	15.6	17.3
QT _c	2.7	0.7	-7.5	-1.8	5.0	1.2	14.7	3.7

* Change and percent change based on mean baseline values for each treatment group. In any individual patient, the above ECG changes cannot be readily used to predict either efficacy or plasma concentration.

Rytmonorm causes a dose-related and concentration related decrease in rate of single and multiple PVCs and can suppress recurrence of ventricular tachycardia. Based on the percent of patients attaining substantial (80-90%) suppression of ventricular ectopic activity, it appears that trough plasma levels of 0.2 to 1.5 µg/mL can provide good suppression, with higher concentrations giving a greater rate of good response.

Haemodynamics:

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure and its inhibition by the beta blockade products by Rytmonorm may in itself aggravate congestive heart failure. Additionally, like other class IC antiarrhythmic drugs, studies in humans have shown that Rytmonorm exerts a negative inotropic effect on the myocardium. Cardiac catheterisation studies in patients with moderately impaired ventricular function (mean C.I. = 2.61 L/min/m²) utilising intravenous propafenone infusions (2mg/kg over 10 min + 2mg/min for 30 min that gave mean plasma concentrations of 3.0µg/mL (well above the therapeutic range of 0.2 - 1.5µg/mL) showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac output and cardiac index.

Pharmacokinetics

Rytmonorm is nearly completely absorbed after oral administration with peak plasma levels occurring approximately 3.5 hours after administration in most individuals. Propafenone exhibits extensive saturable presystemic biotransformation (first pass effect) resulting in a dose dependent and dosage form dependent absolute bioavailability e.g., a 150mg tablet had absolute bioavailability of 3.4%, while a 300mg tablet had absolute bioavailability of 10.6%. A 300 mg solution which was rapidly absorbed, had absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability increased still further. Decreased liver function also increased bioavailability; bioavailability is inversely related to indocyanine green clearance reaching 60-70% at clearances of 7 mL/min and below. The clearance of propafenone is reduced

and the elimination half-life increased in patients with significant hepatic dysfunction (see PRECAUTIONS).

Rytmonorm follows a nonlinear pharmacokinetic disposition presumably due to saturation of first pass hepatic metabolism as the liver is exposed to higher concentrations of propafenone and shows a very high degree of interindividual variability. For example, for a three-fold increase in daily dose from 300 to 900 mg/day there is a ten-fold increase in steady-state plasma concentration. The top 25% of patients given 375mg/day, however, had, a mean concentration of propafenone larger than the bottom 25%, and about equal to the second 25%, of patients given a dose of 900mg. Although food increased peak blood level and bioavailability in a single dose study, during multiple dose administration of propafenone to healthy volunteers food did not change bioavailability significantly.

There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolised with an elimination half-life from 2-10 hours. These patients metabolise propafenone into two active metabolites: 5-hydroxypropafenone, which is formed by CYP2D6, and N-de-propylpropafenone, which is formed by both CYP3A4 and CYP1A2. In vitro preparations have shown these two metabolites to have antiarrhythmic activity comparable to propafenone, but in man they both are usually present in concentrations less than 20% of propafenone. Nine additional metabolites have been identified, most in only trace amounts. It is the saturable hydroxylation pathway that is responsible for the nonlinear pharmacokinetic disposition.

In less than 10% of patients (and in any patient also receiving quinidine, see PRECAUTIONS), metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. The estimated propafenone elimination half-life ranges from 10-32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolise debrisoquine and a variety of other drugs (encainide, metoprolol, dextromethorphan). In these patients, the N-depropyl-propafenone occurs in quantities comparable to the levels occurring in extensive metabolisers. In slow metabolisers propafenone pharmacokinetics are linear.

There are significant differences in plasma concentrations of propafenone in slow and extensive metabolisers, the former achieving concentrations 1.5 to 2.0 times those of the extensive metabolisers at daily doses of 675-900 mg/day. At low doses the differences are greater, with slow metabolisers attaining concentrations more than five times that of extensive metabolisers. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolisers, and because steady-state conditions are achieved after 3-4 days of dosing, the recommended dosing regimen is the same regardless of the metabolic status for all patients (poor versus extensive metabolisers). The greater variability in blood levels require that the drug be titrated carefully in all patients with close attention to clinical and ECG evidence of toxicity (see DOSAGE AND ADMINISTRATION).

Indications

For the prophylaxis and treatment of supraventricular extrasystoles and supraventricular tachycardias, and in WPW syndrome. Also for the prophylaxis and treatment of life-threatening documented ventricular arrhythmias, such as sustained ventricular tachycardia. The use of Rytmonorm is not recommended in patients with less severe ventricular arrhythmias, even if the patients are symptomatic. Because of the proarrhythmic effects of Rytmonorm, its use should be reserved for patients in whom, in the opinion of the physician, the potential benefits of treatment outweigh the risks.

Contraindications

Rytmonorm is contraindicated in the presence of:-

- Known hypersensitivity to the active ingredient, propafenone hydrochloride, or to any of the other ingredients
- Known Brugada Syndrome

- Significant structural heart disease such as:
 - uncontrolled congestive heart failure where left ventricular output is less than 35%
 - cardiogenic shock, unless this is caused by arrhythmia
- severe symptomatic bradycardia
- the presence of sinus node dysfunction, atrial conduction defects, second degree or greater atrioventricular block or bundle branch block or distal block in the absence of an artificial pacemaker
- severe hypotension
- bronchospastic disorders
- manifest electrolyte imbalance (eg potassium metabolism disorders)
- severe obstructive pulmonary disease
- myasthenia gravis
- Patients who are concomitantly taking ritonavir and propafenone hydrochloride (see Drug Interactions)

Precautions

It is essential that each patient given Rytmonorm be evaluated electrocardiographically and clinically prior to and during therapy to determine whether the response to Rytmonorm supports continued treatment.

Brugada Syndrome

A Brugada syndrome may be unmasked or Brugada like electrocardiogram (ECG) changes may be provoked after exposure to Rytmonorm in previously asymptomatic carriers of the syndrome. After initiating therapy with Rytmonorm, an ECG should be performed to rule out changes suggestive of Brugada syndrome.

Mortality

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicentered, randomised, double-blind study in patients with asymptomatic non-life-threatening arrhythmias who had had myocardial infarctions more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of these results to other populations (.e.g., those without recent myocardial infarctions) or to other antiarrhythmic drugs is uncertain, but at present it is prudent to consider any antiarrhythmic agent to have a significant risk in patients with structural heart disease.

Proarrhythmic Effects

Rytmonorm like other antiarrhythmic agents, may cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., tachycardia that is more sustained or more rapid which may lead to fatal consequences. It is therefore essential that each patient given Rytmonorm be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to Rytmonorm supports continued treatment.

Overall in clinical trials with propafenone, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had a worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign

arrhythmias, which included patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see above) suggest that an increased risk is present throughout treatment.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema, asthma):

Patients with bronchospastic diseases or obstruction of the airways, should in general not receive propafenone or other agents with beta-adrenergic-blocking activity.

Congestive Heart Failure

During treatment with oral propafenone in patients with depressed baseline function (mean EF=33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients; of those 0.9% were considered probably or definitely related to Rytmonorm. Of the patients with congestive heart failure probably related to propafenone, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to Rytmonorm developed rarely (< 0.2%) in patients who had no previous history of CHF. As Rytmonorm exerts both beta blockade and a (dose-related) negative inotropic effect on cardiac muscle, patients with congestive heart failure should be fully compensated before receiving Rytmonorm. If congestive heart failure worsens, Rytmonorm should be discontinued (unless congestive heart failure is due to the cardiac arrhythmia) and, if indicated, restarted at a lower dosage only after adequate cardiac compensation has been established.

Conduction Disturbances

Rytmonorm slows atrioventricular conduction and also causes first degree AV block. Average PR interval prolongation and increases in QRS duration are closely correlated with dosage increases and concomitant increases in propafenone plasma concentrations. This incidence of first degree, second degree, and third degree AV block observed in 2,127 patients was 2.5%, 0.5% and 0.2% respectively. Development of second or third degree AV block requires a reduction in dosage or discontinuation of Rytmonorm. Bundle branch block (1.2%) and intraventricular conduction delay (1.1%) have been reported in patients receiving propafenone. Bradycardia has also been reported (1.5%). Experience in patients with sick sinus node syndrome is limited and these patients should not be treated with propafenone.

Effects on Pacemaker Threshold

Rytmonorm may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during the therapy.

Haematologic Disturbances

One case of agranulocytosis with fever and sepsis probably related to the use of propafenone was seen in US clinical trials. The agranulocytosis appeared after 8 weeks of therapy. Propafenone therapy was stopped and the white cell count had normalised by 14 days. The patient recovered. In the course of over 800,00 patients years during marketing outside the U.S. since 1978, seven additional cases have been reported. In one of these, concomitant captopril, a drug known to cause agranulocytosis was used. Unexplained fever and/or decrease in a white cell count particularly during the first three months of therapy warrant consideration of possible agranulocytosis/granulocytopenia. Patients should be instructed to promptly report the development of any signs of infection such as fever, sore throat or chills.

Hepatic Dysfunction

Propafenone is highly metabolised by the liver and should therefore, be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction increases the bioavailability of propafenone to approximately 70% compared to 3-40% for patients with normal liver function. In eight patients with moderate to severe liver disease, the mean half-life was approximately 9 hours. As a result, the dose of propafenone given to patients with impaired hepatic function should be approximately 20-30% of the dose given to patients with normal hepatic function. Careful monitoring for excessive pharmacological effects (see OVERDOSAGE) should be carried out.

Renal Dysfunction

A considerable percentage of propafenone metabolites (18.5%-38%) of the dose/48 hours) are excreted in the urine. Until further data are available, Rytmonorm (propafenone HCl) should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (see OVERDOSAGE).

Elevated ANA Titers

Positive ANA Titers have been reported in patients receiving propafenone. They have been reversible upon cessation of treatment and may disappear even in the face of continued propafenone therapy. These laboratory findings were usually not associated with clinical symptoms, but there is one published case of drug-induced lupus erythematosus (positive rechallenge); it resolved completely upon discontinuation of therapy. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

Impaired Spermatogenesis

Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose intravenous administration. Evaluation of the effects of short-term propafenone administration on spermatogenesis in 11 normal subjects suggest that propafenone produces a reversible short-term drop (within normal range) in sperm count. Subsequent evaluation in 11 patients receiving propafenone chronically have suggested no effect of propafenone on sperm count.

Effects on Fertility

Use in Pregnancy

There are no adequate and well-controlled studies in pregnant women. Propafenone hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Propafenone hydrochloride is known to pass the placental barrier in humans. The concentration of propafenone in the umbilical cord has been reported to be about 30% of that in the maternal blood.

It is not known whether the use of propafenone during labour or delivery has immediate or delayed adverse effects on the foetus, or whether it prolongs the duration of labour or increases the need for forceps delivery or other obstetrical intervention.

Use in Lactation

Excretion of propafenone hydrochloride in human breast milk has not been studied. Limited data suggests that propafenone hydrochloride may be excreted in human breast milk. Propafenone hydrochloride should be used with caution in nursing mothers.

Paediatric Use

The safety and efficacy of Rytmonorm in children has not been established.

Use in the Elderly

There do not appear to be any age related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, Rytmonorm should be used with caution. The effective dose may be lower in these patients.

Carcinogenicity

Lifetime maximally tolerated oral dose studies in mice (up to 80 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propafenone.

Genotoxicity

Propafenone was not mutagenic when assayed for genotoxicity in:

- 1) mouse dominant lethal test;

- 2) rat bone marrow chromosome analysis;
- 3) Chinese hamster bone marrow and spermatogonia chromosome analysis;
- 4) Chinese hamster micronucleous test; and
- 5) Ames bacterial test.

Propafenone administered intravenously to rabbits, dogs and monkeys has been shown to decrease spermatogenesis. These effects were reversible, were not found following oral dosing of propafenone, were seen only at lethal or sublethal dose levels and were not seen in rats treated either orally or intravenously (see PRECAUTIONS). Propafenone did not affect either male or female fertility rates when administered intravenously to rats and rabbits at dose levels up to 18 times the maximum recommended daily human dose of 900mg (based on 60kg human body weight).

Effect on ability to drive and use machinery

It is important to note that blurred vision, dizziness, fatigue or orthostatic hypotension may affect the patient's speed of reaction to the point where the patient's ability to operate machinery or motor vehicles is impaired.

Interactions with other Medicines

Quinidine

Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolisers (see ACTIONS). There is, as yet, too little information to recommend concomitant use of propafenone and quinidine.

Local Anaesthetics

Concomitant use of local anaesthetics (i.e., during pacemaker implantation, surgery, or dental use) may increase the risks of central nervous system side effects.

Digitalis

Rytmonorm produces dose-related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day of propafenone without affecting digoxin renal clearance. These elevations of digoxin levels were maintained for up to 16 months during concomitant administration. Plasma digoxin levels of patients on concomitant therapy should be measured, and digoxin dosage should ordinarily be reduced when propafenone is started, especially if a relatively large digoxin dose is used or if plasma concentrations are relatively high.

Beta-Antagonists

In a study involving healthy subjects, concomitant administration of propafenone and propranolol has resulted in substantial increases in propranolol plasma concentration and elimination half-life with no change in propafenone plasma levels from control values. Similar observations have been reported with metoprolol. Propafenone appears to inhibit the hydroxylation pathway for the two beta-antagonists (just as quinidine inhibits propafenone metabolism). Increased plasma concentrations of metoprolol could overcome its relative cardioselectivity. In propafenone clinical trials, patients who were receiving beta-blockers concurrently did not experience an increased incidence of side effects. While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone.

Warfarin

In a study of eight healthy subjects receiving propafenone and warfarin concomitantly, mean steady-state warfarin plasma concentration increased 39% with a corresponding increase in prothrombin times of approximately 25%.

Close monitoring of the clotting status in patients receiving concomitant oral anticoagulants is recommended as Rytmonorm may enhance the efficacy of these drugs resulting in increased prothrombin time.

Cimetidine

Concomitant administration of Rytmonorm and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentration of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone.

Ritonavir

Due to the potential for increased plasma concentrations, co-administration of ritonavir and Rytmonorm is contraindicated (see **CONTRAINDICATIONS**).

Other

Limited experience with propafenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions.

If Rytmonorm is administered with phenobarbital or rifampicin, propafenone plasma concentrations might decrease (possibly to sub-therapeutic range).

Drugs that inhibit CYP2D6, CYP1A2 and CYP3A4, e.g. ketoconazole, cimetidine and quinidine, erythromycin and grapefruit juice might lead to increased levels of propafenone hydrochloride. When propafenone hydrochloride is administered with inhibitors of these enzymes, the patients should be closely monitored and the dose adjusted accordingly.

Coadministration of Rytmonorm with drugs metabolized by CYP2D6 (such as venlafaxine) might lead to increased levels of these drugs. Increases in propranolol, metoprolol, desipramine, cyclosporine, theophylline and digoxin plasma levels or blood levels have been reported during Rytmonorm therapy.

Combination therapy of amiodarone and Rytmonorm can affect conduction and repolarisation and lead to abnormalities that have the potential to be proarrhythmic. Dose adjustments of both compounds based on therapeutic response may be required.

No significant effects on the pharmacokinetics of Rytmonorm or lidocaine have been seen following their concomitant use in patients. However, concomitant use of Rytmonorm and intravenous lidocaine have been reported to increase the risks of central nervous system side effects of lidocaine.

Elevated levels of plasma propafenone may occur when Rytmonorm is used concomitantly with SSRIs, such as fluoxetine and paroxetine. Concomitant administration of Rytmonorm and fluoxetine in extensive metabolisers increased the S propafenone C_{max} and AUC by 39 and 50% and the R propafenone C_{max} and AUC by 71 and 50%. Lower doses of Rytmonorm may be sufficient to achieve the desired therapeutic response.

Adverse Effects

Adverse reactions associated with Rytmonorm (propafenone HCl) occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. About 20% of patients discontinued due to adverse reactions. Results of controlled trials comparing adverse reactions rates on propafenone and placebo, and on propafenone and quinidine are shown in the following table. Adverse reactions appearing in the table were reported for $\geq 1\%$ of the patients receiving propafenone. The most common events were dizziness, unusual taste, first degree AV block, intraventricular conduction delay, nausea and/or vomiting, and constipation. Headache was relatively common also, but was not increased compared to placebo.

Adverse Reactions Reported For \geq 1% Of Patients

	Prop/Placebo Trials		Prop/Quinoline Trial	
	Prop (N=247) (%)	Placebo (N=111) (%)	Prop (N=53) (%)	Quinidine (N=52) (%)
Unusual taste	7.3	0.9	22.6	0.0%
Dizziness	6.5	5.4	15.1	9.6
First Degree AV Block	4.5	0.9	1.9	0.0
Headache(s)	4.5	4.5	1.9	7.7
Constipation	4.0	0.0	5.7	1.9
Intraventricular Conduction Delay	4.0	0.0	-	-
Nausea and/or Vomiting	2.8	0.9	5.7	15.4
Fatigue	-	-	3.8	1.9
Palpitations	2.4	0.9	-	-
Blurred Vision	2.0	0.9	5.7	1.9
Dry Mouth	2.0	0.9	5.7	5.8
Dyspnoea	2.0	2.7	3.8	0.0
Abdominal Pain/Cramps	-	-	1.9	7.7
Dyspepsia	-	-	1.9	7.7
Congestive Heart Failure	-	-	1.9	0.0
Fever	-	-	1.9	9.6
Tinnitus	-	-	1.9	1.9
Vision Abnormal	-	-	1.9	1.9

Adverse Reactions Reported for \geq 1% of Patients

	Prop/Placebo Trials			
	Prop (N=247) (%)	Placebo (N=111) (%)	Prop (N=53) (%)	Quinidine (N=52) (%)
Oesophagitis	-	-	1.9	0.0
Gastroenteritis	-	-	1.9	0.0
Anxiety	2.0	1.8	-	-
Anorexia	1.6	0.9	-	1.9
Proarrhythmia	1.2	0.0	1.9	0.0
Flatulence	1.2	0.0	1.9	0.0
Angina	1.2	0.0	1.9	3.8
Second Degree AV Block	1.2	0.0	-	-
Bundle Branch Block	1.2	0.0	1.9	1.9
Loss of Balance	1.2	0.0	-	-
Diarrhoea	1.2	0.9	5.7	38.5

Adverse reactions reported for $\geq 1\%$ of 2127 patients who received propafenone in U.S. clinical trials are presented in the following table by propafenone daily dose. The most common adverse reactions in controlled clinical trial appeared dose related (but note that most patients spent more time at the larger doses), especially dizziness, nausea and/or vomiting, unusual taste, constipation, and blurred vision. Some less common reactions may also have been dose related such as first degree AV block, congestive heart failure, dyspepsia, and weakness. The principle causes of discontinuation were the most common events and are shown in the following table

Adverse Reactions Reported for $\geq 1\%$ of patients N=2127

	Incidence by Total Daily Dose				
	450mg (N=1430) (%)	600mg (N=1337) (%)	≥ 900 mg (N=1333) (N=2127) (%)	Total Incidence Who Discontinued (%)	% of Pts
Dizziness	3.6	6.6	11.0	12.5	2.4
Nausea and/or Vomiting	2.4	6.1	8.9	10.7	3.4
Unusual Taste	2.5	4.9	6.3	8.8	0.7
Constipation	2.0	4.1	5.3	7.2	0.5
Fatigue	1.8	2.8	4.1	6.0	1.0
Dyspnoea	2.2	2.3	3.6	5.3	1.6
Proarrhythmia	2.0	2.1	2.9	4.7	4.7
Angina	1.7	2.1	3.2	4.6	0.5
Headache(s)	1.5	2.5	2.8	4.5	1.0
Blurred Vision	0.6	2.4	3.1	3.8	0.8
CHF	0.8	2.2	2.6	3.7	1.4
Ventricular Tachycardia	1.4	1.6	2.9	3.4	1.2
Dyspepsia	1.3	1.7	2.5	3.4	0.9
Palpitations	0.6	1.6	2.6	3.4	0.5%
Rash	0.6	1.4	1.9	2.6	0.8
AV Block, First Degree	0.8	1.2	2.1	2.5	0.3
Diarrhoea	0.5	1.6	1.7	2.5	0.6
Weakness	0.6	1.6	1.7	2.4	0.7
Dry Mouth	0.9	1.0	1.4	2.4	0.2
Syncope/Near Syncope	0.8	1.3	1.4	2.2	0.7
QRS Duration, Increased	0.5	0.9	1.7	1.9	0.5
Chest Pain	0.5	0.7	1.4	1.8	0.2
Anorexia	0.5	0.7	1.6	1.7	0.4
Abdominal Pain/Cramps	0.8	0.9	1.1	1.7	0.4

Adverse Reactions from Postmarketing Surveillance or Clinical Trials

Adverse events have been reported during post-approval use of Rytmonorm. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Rytmonorm exposure.

The following adverse events have been reported with this or other formulations of Rytmonorm.

Body System	Adverse Reaction
Blood and lymphatic system disorders	Bruising Increased bleeding time Leukocytopenia Granulocytopenia Thrombocytopenia; Agranulocytosis Anaemia Purpura
Immune system disorders	Positive ANA test Allergic reactions
Metabolism and nutrition disorders	Anorexia
Psychiatric disorders	Anxiety Confusion
Nervous system disorders	Abnormal dreams Abnormal speech Abnormal vision Apnoea Coma Depression Memory loss Numbness Psychosis / mania Seizures Tinnitus Unusual smell sensation Syncope Paresthesia Vertigo Ataxia Headache Dizziness
Eye disorders	Eye irritation Blurred vision
Cardiac disorders	Atrial flutter AV dissociation Cardiac arrest Flushing Hot flashes Sic sinus syndrome

Body System	Adverse Reaction
	<p>Sinus pause or arrest Supraventricular tachycardia A marked reduction in heart rate (bradycardia) or conduction disorders (i.e., atrioventricular or intraventricular block) may occur.</p> <p>Proarrhythmic effects, which manifest as an increase in heart rate (tachycardia), or ventricular fibrillation may also occur.</p>
Vascular disorders	Hypotension, including postural hypotension and orthostatic hypotension
Gastrointestinal disorders	<p>Gastroenteritis Nausea Vomiting Constipation Dry mouth Bitter taste Abdominal pain</p>
Hepatobiliary disorders	Liver abnormalities, including hepatocellular injury, cholestasis, jaundice and hepatitis
Skin and subcutaneous tissue disorders	<p>Alopecia Pruritus Reddening of the skin Itching Urticaria Rash</p>
Musculoskeletal and connective tissue disorders	<p>Muscle cramps Muscle weakness Lupus (erythematosus) syndrome</p>
Renal and urinary disorders	<p>Kidney failure Nephrotic syndrome</p>
Reproductive system and breast disorders	Impotence
General disorders and administration site conditions	<p>Fatigue Chest pain</p>
Investigations	<p>Hyponatremia / inappropriate ADH secretion Increased glucose Elevated liver enzymes (serum transaminases and alkaline phosphatase)</p>

Dosage and Administration

The use of Rytmonorm should be initiated by a specialist physician. The individual maintenance dose should be determined under cardiological surveillance including repeated ECG monitoring and repeated blood pressure control (titration phase). If the QRS interval is prolonged by more than 20% or the corrected QT interval is lengthened, the dose should be reduced or discontinued until the ECG returns to normal.

For initial and maintenance treatment a daily dose of 450-600mg (1 film-coated tablet of Rytmonorm 150mg 3 times daily or up to 1 film coated tablet of Rytmonorm 300mg twice daily) is recommended. Occasionally an increase of the daily dose to 900mg may be necessary (1 film-coated tablet of Rytmonorm 300mg or 2 film-coated tablets of Rytmonorm 150mg 3 times a day). This daily dose should be exceeded only in exceptional cases and under strict cardiological control.

This data applies to patients with a body weight of about 70kg. The daily doses are to be reduced accordingly for patients weighting less (e.g. two thirds of the dosage in patients with a body weight of approximately 50kg). Dose increases should not be attempted until the patient has been receiving treatment for three to four days.

No overall differences in safety or effectiveness were observed in the geriatric patient population, but greater sensitivity of some older individuals cannot be ruled out, therefore, these patients should be carefully monitored. The same applies to maintenance therapy.

During the initial phase of treatment in the elderly or in patients with myocardial damage the dose of Rytmonorm should, as with other anti-arrhythmic agents, be increased gradually and with special care.

Because of their bitter taste and surface anaesthetic action the tablets should be swallowed whole with some liquid after meals.

Overdosage

The symptoms of overdosage, which are usually most severe within 3 hours of ingestion, may include hypotension, somnolence, bradycardia, intra-atrial and intraventricular conduction disturbances, and rarely convulsions, death and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam. General supportive measures such as mechanical respiratory assistance and external cardiac massage may be necessary.

Contact the Poisons Information Centre 0800 764 766 for advice on management of overdosage.

Owing to high protein binding (>95%) and the large volume of distribution, haemodialysis is ineffective and attempts to achieve elimination via haemoperfusion are of limited efficacy.

General supportive measures and medication for symptomatic treatment as defined in treatment guidances may be necessary.

Presentation and Storage Conditions

Rytmonorm 150mg: white to off-white, round, biconvex film coated tablets embossed on one face with "150", with the "Knoll triangle" below. The other face is unmarked. Foil-backed blister platforms of 10 tablets. Rytmonorm 150 mg is available in packs of 50 tablets.

Rytmonorm 300mg: white to off-white round, biconvex, film-coated tablets embossed on one face with "300" above a scoreline, and the "Knoll Triangle" below. The other face is scored. Foil-backed blister platforms containing 10 tablets. Rytmonorm 300 mg is available in packs of 50 tablets.*

* Rytmonorm 300mg tablets are not currently marketed in New Zealand

Further Information

Nil

Name and Address of the Sponsor

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New Zealand

Medicine Schedule

Prescription Medicine

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