

RYTMONORM®

1. Product Name

Rytmonorm, 150 mg, film coated tablets.

2. Qualitative and Quantitative Composition

Each Rytmonorm film coated tablet contains 150 mg of propafenone (as propafenone hydrochloride).

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Rytmonorm 150 mg - white to off-white, round, biconvex film coated tablets embossed on one face with "150". The other face is unmarked.

4. Clinical Particulars

4.1 Therapeutic indications

For the treatment of supraventricular extrasystoles and supraventricular tachycardias, and in Wolff-Parkinson-White (WPW) syndrome. Also for the treatment of life-threatening documented ventricular tachyarrhythmia.

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.

4.2 Dose and method of administration

Dose

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 widened by more than 20%, the corrected QT interval is lengthened or second or third degree AV block occurs, the dose should be reduced or discontinued until the ECG returns to normal.

The dosage is to be adjusted to the individual patient's requirements.

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.

Adults

For initial and maintenance treatment a daily dose of 450 to 600 mg (1 film-coated tablet of Rytmonorm 150 mg 3 times daily or up to 2 film coated tablets of Rytmonorm 150 mg twice daily) is recommended.

Occasionally an increase of the daily dose to 900 mg may be necessary (2 film-coated tablets of Rytmonorm 150 mg 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 70 kg. The daily doses are to be reduced accordingly for patients weighing less (e.g. two thirds of the dosage in patients with a body weight of approximately 50 kg). Dose increases should not be attempted until the patient has been receiving treatment for three to four days.

Special populations

Paediatric

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

Elderly

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. Any dose increases that may be required should not be undertaken until after five to eight days of therapy.

Hepatic and/or renal impairment

In patients whose liver and/or kidney function is impaired, there may be drug accumulation after standard therapeutic doses. Nonetheless, patients with these conditions can still be titrated on propafenone hydrochloride under ECG and clinical monitoring. The dose of propafenone given to patients with impaired hepatic function should be approximately 20 to 30% of the dose given to patients with normal hepatic function.

Method of administration

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

4.3 Contraindications

Rytmonorm is contraindicated in the presence of:

- Known hypersensitivity to the active ingredient, propafenone hydrochloride, or to any of the excipients listed in section 6.1
- Known Brugada Syndrome (see section 4.4)
- Myocardial infarction within previous 3 months
- 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 (e.g. potassium metabolism disorders)
- Severe obstructive pulmonary disease

- Myasthenia gravis
- Patients who are concomitantly taking ritonavir and propafenone hydrochloride (see section 4.5).

4.4 Special warnings and precautions for use

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 worsen pre-existing arrhythmias (see section 4.8). 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.

Non-allergic 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.

Heart disease

As with other class 1c anti-arrhythmic agents, patients with significant structural heart disease may be predisposed to serious adverse effects. Therefore, propafenone hydrochloride is contraindicated in these patients (see section 4.3).

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.

There is the potential for conversion of paroxysmal atrial fibrillation to atrial flutter with accompanying 2:1 conduction block or 1:1 conduction (see section 4.8).

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 to 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 to 30% of the dose given to patients with normal hepatic function. Careful monitoring for excessive pharmacological effects (see section 4.9) should be carried out.

Renal dysfunction

A considerable percentage of propafenone metabolites (18.5% to 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 section 4.9).

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.

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.

Interference with laboratory tests

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.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Quinidine

Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolisers (see section 5.2). When propafenone hydrochloride is administered with quinidine, the patient should be closely monitored and the dose adjusted accordingly.

Local anaesthetics

A possible potentiation of drug side effects may occur when propafenone hydrochloride is taken in conjunction with local anaesthetics (e.g., pacemaker implantation, surgery or dental work) and other drugs which have an inhibitory effect on the heart rate and/or myocardial contractility.

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.

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

A possible potentiation of drug side effects may occur when propafenone hydrochloride is taken in conjunction with drugs which have an inhibitory effect on the heart rate and/or myocardial contractility (e.g. beta blockers).

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. While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone.

Anticoagulants

Close monitoring of the clotting status in patients receiving concomitant oral anticoagulants (e.g. phenprocoumon, warfarin) is recommended as Rytmonorm may enhance the efficacy of these drugs resulting in increased prothrombin time. Doses of these medicinal products should be reduced, as appropriate, if signs of overdose are observed.

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%.

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. When propafenone hydrochloride is administered with cimetidine, the patient should be closely monitored, and the dose adjusted accordingly.

Ritonavir

Due to the potential for increased plasma concentrations, co-administration of ritonavir and Rytmonorm is contraindicated (see section 4.3).

Other

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

Concomitant use of propafenone hydrochloride and rifampin may reduce the antiarrhythmic efficacy of propafenone hydrochloride as the result of a reduction in the propafenone plasma levels.

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

Phenobarbital is a known inducer of CYP3A4. Response to propafenone hydrochloride therapy should be monitored during concomitant chronic phenobarbital use.

Co-administration of Rytmonorm with drugs metabolized by CYP2D6 (such as venlafaxine) might lead to increased levels of these drugs. Increases in desipramine, ciclosporine and theophylline plasma levels or blood levels have been reported during Rytmonorm therapy. Doses of these medicinal products should be reduced, as appropriate, if signs of overdose are observed.

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.

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.

A possible potentiation of drug side effects may occur when propafenone hydrochloride is taken in conjunction with drugs which have an inhibitory effect on the heart rate and/or myocardial contractility (e.g. tricyclic antidepressants).

4.6 Fertility, pregnancy and lactation

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.

Breast-feeding

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.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

It is important to note that blurred vision, dizziness, fatigue or postural 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.

4.8 Undesirable effects

The most common events were dizziness, cardiac conduction disorders and palpitations. About 20% of patients discontinued due to adverse reactions. Results from controlled trials and post-marketing experience with propafenone are shown below.

The reactions are displayed by MedDRA system organ class and frequency using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) and not known (adverse reactions from post-marketing experience with this or other formulations of Rytmonorm; frequency cannot be estimated from the available data). Within each frequency grouping, adverse effects are presented in order of decreasing seriousness when the seriousness could be assessed.

Blood and lymphatic system disorders

Uncommon	Thrombocytopenia
Not known	Agranulocytosis, leukopenia, granulocytopenia, anemia, bruising, increased bleeding time, leukocytopenia, purpura

Immune system disorders

Not known	Hypersensitivity ¹ , positive ANA test
-----------	---

Metabolism and nutrition disorders

Common	Anorexia
Uncommon	Decreased appetite

Psychiatric disorders

Common	Anxiety, sleep disorders
Uncommon	Nightmare
Not known	Confusional state

¹ May be manifested by cholestasis, blood dyscrasias, and rash.

Nervous system disorders

Very common	Dizziness ²
Common	Headache, dysgeusia, weakness
Uncommon	Syncope, Ataxia, Paresthesia
Not known	Convulsion, extrapyramidal symptoms, restlessness, abnormal dreams, abnormal speech, abnormal vision, apnoea, coma, depression, memory loss, numbness, psychosis/mania, seizures, tinnitus, unusual smell sensation

Eye disorders

Common	Vision blurred
Not known	Eye irritation

Ear and labyrinth disorders

Uncommon	Vertigo
----------	---------

Cardiac disorders

Very common	Cardiac conduction disorders ³ , palpitations
Common	Sinus bradycardia, bradycardia, tachycardia, atrial flutter, AV dissociation/block, angina, congestive heart failure, QRS interval prolonged
Uncommon	Ventricular tachycardia, arrhythmia ⁴
Not known	Ventricular fibrillation, cardiac failure ⁵ , heart rate reduced, flushing, hot flushes, sick sinus syndrome, supraventricular tachycardia

Vascular disorders

Uncommon	Hypotension
Not known	Orthostatic hypotension including postural hypotension

Respiratory, thoracic and mediastinal disorders

Common	Dyspnea
--------	---------

Gastrointestinal disorders

Common	Abdominal pain, vomiting, nausea, diarrhea, constipation, dry mouth, dyspepsia
Uncommon	Abdominal distension, flatulence
Not known	Retching, gastrointestinal disturbance, gastroenteritis

Hepatobiliary disorders

Common	Hepatic function abnormal ⁶
Not known	Hepatocellular injury, cholestasis, hepatitis, jaundice

Skin and subcutaneous tissue disorders

Uncommon	Urticaria, pruritus, rash, erythema
Not known	Alopecia, acute generalised exanthematous pustulosis

Musculoskeletal and connective tissue disorders

Not known	Lupus-like syndrome, muscle cramps, muscle weakness
-----------	---

Reproductive system and breast disorders

² Excluding vertigo.

³ Including sinoatrial block, atrioventricular block and intraventricular block.

⁴ Propafenone may be associated with proarrhythmic effects which manifest as an increase in heart rate (tachycardia) or ventricular fibrillation. Some of these arrhythmias can be life-threatening and may require resuscitation to prevent a potentially fatal outcome.

⁵ An aggravation of preexisting cardiac insufficiency may occur.

⁶ This term covers abnormal liver function tests, such as aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased and blood alkaline phosphatase increased.

Uncommon Erectile dysfunction
Not known Sperm count decreased⁷

General disorders and administration site conditions

Common Chest pain, asthenia, fatigue, pyrexia

Renal and urinary disorders

Not known Kidney failure, nephrotic syndrome

Investigations

Not known Hyponatremia/inappropriate ADH secretion, increased glucose

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Symptoms

Myocardial symptoms

The effects of propafenone hydrochloride overdose in the myocardium manifest as impulse generation and conduction disorders such as PQ prolongation, QRS widening, suppression of sinus node automaticity, AV block, ventricular tachycardia, ventricular flutter, ventricular fibrillation and cardiac arrest. Reduction of contractility (negative inotropic effect) can cause hypotension which, in severe cases, can lead to cardiovascular shock.

Non-cardiac signs and symptoms

Metabolic acidosis, headache, dizziness, blurred vision, paraesthesia, tremor, nausea, constipation, dry mouth and convulsions have been reported on overdose.

Death has also been reported.

In severe cases of poisoning, tonic-clonic convulsions, paraesthesia, somnolence, coma and respiratory arrest may occur.

Treatment

In addition to general emergency measures, the patient's vital parameters should be monitored in an intensive care setting, and rectified, as appropriate.

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.

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.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

⁷ Decreased sperm count is reversible upon discontinuation of propafenone.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiarrhythmics, class 1c,

ATC code: C01BC03.

Rytmonorm (propafenone hydrochloride) is a class 1c antiarrhythmic drug with some structural similarities to beta-blocking agents.

Mechanism of action

Propafenone hydrochloride is an antiarrhythmic agent with membrane-stabilizing, sodium channel blocking properties (Vaughan Williams, class 1c). It also possesses weak beta blocking efficacy (class II according to Vaughan Williams). Propafenone hydrochloride reduces the rate of rise of the action potential thereby slowing down impulse conduction (negative dromotropic effect). The refractory periods in the atrium, atrioventricular (AV) node and ventricles are prolonged. Propafenone hydrochloride prolongs the refractory periods in the accessory pathways in patients with WPW syndrome.

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.

Mean Changes in ECG Intervals*								
Total Daily Dose (mg)								
	337.5 mg		450 mg		675 mg		900 mg	
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 to 90%) suppression of ventricular ectopic activity, it appears that trough plasma levels of 0.2 to 1.5 microg/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 1c 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 (2 mg/kg over 10 min + 2 mg/min for 30 min that gave mean plasma concentrations of 3.0 microg/mL (well above the therapeutic range of 0.2 to 1.5 microg/mL) showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac output and cardiac index.

Clinical efficacy and safety

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.

5.2 Pharmacokinetic properties

Propafenone is a racemic mixture of S- and R-propafenone.

Absorption

Rytmonorm is nearly completely absorbed after oral administration with peak plasma levels occurring approximately two to three hours after administration in most individuals. Although food increased the maximal plasma concentration and bioavailability in a single dose study, during multiple dose administration of propafenone to healthy subjects, food did not change bioavailability significantly.

Distribution

Propafenone distributes rapidly. The steady-state volume of distribution is 1.9 to 3.0 L/kg. The degree of plasma protein binding of propafenone is concentration dependent and decreased from 97.3% at 0.25 microg/mL to 81.3% at 100 microg/mL.

Biotransformation

Propafenone is known to undergo extensive and saturable presystemic biotransformation (CYP2D6 hepatic first pass effect) which results in a dose- and dosage form dependent absolute bioavailability e.g., a 150 mg tablet had absolute bioavailability of 3.4%, while a 300 mg 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 to 70% at clearances of 7 mL/min and below.

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 two to ten hours (extensive metabolizers). These patients metabolise propafenone into two active metabolites: 5-hydroxypropafenone, which is formed by CYP2D6, and N-depropyl-propafenone (norpropafenone), 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 section 4.4), metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed (i.e. poor metabolizers). 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 to 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 section 4.2).

Elimination

The estimated propafenone elimination half-life ranges from 2 to 10 hours for extensive metabolizers and from 10 to 32 hours for poor metabolizers. Clearance of propafenone is 0.67 to 0.81 L/h/kg.

The clearance of propafenone is reduced and the oral bioavailability and the elimination half-life are increased in patients with hepatic dysfunction (see sections 4.2 and 4.4).

Linearity/non-linearity

In slow metabolizers, propafenone pharmacokinetics are linear.

In extensive metabolizers, Rytmonorm follows a nonlinear pharmacokinetic disposition presumably due to saturation of first pass hepatic metabolism (hydroxylation pathway, CYP2D6) as the liver is exposed to higher concentrations of propafenone. 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 375 mg/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 900 mg.

Inter/intra individual variability

With propafenone hydrochloride, there is a considerable degree of individual variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear pharmacokinetics in extensive metabolizers. The large variability in blood levels requires that the dose be titrated carefully in patients, paying close attention to clinical and electrocardiographic evidence of toxicity. Elderly population

Propafenone exposure in elderly subjects with normal renal function was highly variable, and not significantly different from healthy young subjects. Exposure to 5-hydroxypropafenone was similar, but exposure to propafenone glucuronides was doubled.

Renal impairment

In patients with renal impairment, exposure to propafenone and 5-hydroxypropafenone was similar to that in healthy controls, while accumulation of glucuronide metabolites was observed. Propafenone hydrochloride should be administered cautiously in patients with renal disease.

Hepatic impairment

Propafenone shows an increased oral bioavailability and half-life in patients with liver impairment. The dosage must be adjusted in patients with liver disease.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction.

Studies in anaesthetised dogs and isolated organ preparations show that Rytmonorm has beta-sympatholytic activity at about 1/50 of potency of propranolol.

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.

Carcinogenesis, mutagenesis and impairment on fertility

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.

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 micronucleus 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 section 4.4). 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 900 mg (based on 60 kg human body weight).

6. Pharmaceutical Particulars

6.1 *List of excipients*

Rytmonorm 150 mg tablets also contain

- microcrystalline cellulose
- sodium croscarmellose
- starch - pregelatinised
- hypromellose
- magnesium stearate
- macrogol
- titanium dioxide.

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

Rytmonorm 150 mg: 3 years.

6.4 *Special precautions for storage*

Store at or below 25°C.

6.5 *Nature and contents of container*

Blister packs. Pack size of 50 tablets.

6.6 *Special precautions for disposal*

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatrix Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatrix.co.nz
Telephone 0800 168 169

9. Date of First Approval

1 October 1992

10. Date of Revision of the Text

21 January 2022

Summary table of changes

Section	Summary of new information
Header	Updated logo
8	Updated sponsor details
-	Added trademark attribution statement

Rytmonorm® is a Viatrix company trade mark.