1. TRADE NAME OF THE MEDICINAL PRODUCT

RYTMONORM 150 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg propafenone HCl.
Excipients: Each 150 mg tablet contains up to 10.0 mg sodium.

3. PHARMACEUTICAL FORM

White to off white film coated tablets,: Face 1: "150"; Face 2-none

4. CLINICAL PARTICULARS

4.1.Therapeutic Indications

Prophylaxis and treatment of ventricular arrhythmias.
Prophylaxis and treatment of atrial fibrillation and flutter.
Prophylaxis and treatment of paroxysmal supraventricular tachycardia (PSVT) associated with disabling symptoms.

4.2. Posology and Method of Administration

Posology
Note:
Patients with ventricular arrhythmias require careful cardiological surveillance at the beginning of propafenone treatment. These patients should only be started on the drug if emergency cardiological equipment is available and if the possibility of monitoring is assured.
The individual maintenance dose should be determined under cardiological surveillance including ECG monitoring and repeated blood pressure control (adjustment phase). A decision should be made as to whether to continue treatment if there are ECG changes such as QRS or QT prolongation greater than 25% or PR prolongation greater than 50% or QT prolongation to more than 500 ms, or an increase in the incidence or severity of cardiac arrhythmias.

Elderly patients:
No overall differences in safety or effectiveness were observed in this 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. In such patients it is recommended to postpone therapeutically necessary dose increases until steady state plasma concentrations have been reached, usually after around 5 to 8 days. This precaution reduces the risk of inducing proarrhythmic effects in these patients during the initial phase of treatment.

In those patients in whom significant widening of the QRS complex or second or third degree AV block occurs, a dose reduction should be considered.

Note: In patients with flutter, treatment should be initiated with careful monitoring (preferably under hospitalization).

When prescribing propafenone it should be taken into account that there is no evidence that antiarrhythmic treatment with Class I antiarrhythmics improves survival.

It is recommended that therapy be initiated with 150 mg propafenone given every eight hours (450 mg/day). Dosage may be increased at a minimum of 3 to 4 day intervals to 300 mg every 12 hours (600 mg/day). If necessary, 300 mg every 8 hours (900 mg/day) may be administered until optimum clinical response is obtained.

Occasionally, it may be necessary to increase the daily dose to 900 mg of propafenone hydrochloride. The daily dose should be reduced accordingly for patients with a lower body weight.
Dose increases should not be attempted until the patient has been receiving treatment for 3-4 days.

The individual maintenance dose should be determined under cardiological surveillance including ECG monitoring and repeated blood pressure control (titration phase).

The usefulness and safety of dosages exceeding 900 mg per day have not been established.

As with other antiarrhythmic agents, in the elderly or in patients with marked previous myocardial damage, the dose of Rytmonorm should be increased slowly and gradually during the initial phase of treatment, whereby monitoring of plasma concentrations of the drug may be appropriate. The first dose increase should take place after 5 to 8 days at the earliest.

Patients with Hepatic/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.
Method of administration
Because of its bitter taste and its surface anaesthetic action, the tablets should be swallowed whole together with some liquid after meals.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Rytmonorm is contraindicated in patients with known Brugada Syndrome (see Special Warnings and Precautions for Use).

Rytmonorm is contraindicated in patients with significant structural heart disease such as patients with an incident of myocardial infarction within the last 3 months, uncontrolled congestive heart failure where left ventricular output is less than 35%, cardiogenic shock (unless arrhythmia-induced), severe symptomatic bradycardia, manifest electrolyte imbalance (e.g., potassium metabolism disorders), severe obstructive pulmonary disease or severe hypotension.

Rytmonorm may worsen myasthenia gravis.

Unless patients are adequately paced (see section 4.4, Special Warnings and Precautions for Use), Rytmonorm should not be used in the presence of sinus node dysfunction, atrial conduction defects, second degree or greater AV block, bundle branch block or distal block.

Due to the potential for increased plasma concentrations, co-administration of ritonavir is contraindicated.

4.4. Special Warnings and Precautions for Use

The weak negative inotropic effect of Rytmonorm may assume importance in patients predisposed to cardiac failure.
In common with other anti-arrhythmic drugs, Rytmonorm has been shown to alter sensitivity and pacing threshold. In patients with pacemakers, appropriate adjustments may be required.

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

Because of the beta-blocking effect, care should be exercised in the treatment of patients with obstructive airways disease e.g., asthma.

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

A Brugada syndrome may be unmasked or Brugada like electrocardiogram (ECG) changes may be provoked after exposure to propafenone in previously

asymptomatic carriers of the syndrome. After initiating therapy with propafenone, as ECG should be performed to rule out changes suggestive of Brugada syndrome.

Propafenone like other antiarrhythmics may cause proarrhythmic effects, i.e., it may cause new or worsen preexisting arrhythmias (see section 4.8). 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.

This medicine contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5. Interactions with other Medicaments and other forms of Interaction

Potential increase in adverse reactions may occur when propafenone is taken in conjunction with local anaesthetics (e.g., pacemaker implantation, surgery or dental work) and other medicinal products which have an inhibitory effect on the heart rate and/or myocardial contractility (e.g., beta blockers, tricyclic antidepressants).

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

Increased plasma levels and/or blood levels of propranolol, metoprolol, desipramine, ciclosporin, theophylline and digoxin have been reported during propafenone therapy. Doses of these medicinal products should be reduced, as appropriate, if signs of overdose are observed. Elevated levels of plasma propafenone may occur when propafenone is used concomitantly with SSRIs, such as fluoxetine and paroxetine. Concomitant administration of propafenone and fluoxetine in extensive metabolisers increases 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 propafenone may therefore be sufficient to achieve the desired therapeutic response.

Close monitoring of the clotting status in patients receiving concomitant oral anticoagulants (e.g., phenprocoumon, warfarin) is recommended as propafenone may enhance the plasma levels of these medicinal products resulting in an increased prothrombin time. Doses of these medicinal products should be adjusted if necessary.

Coadministration of propafenone hydrochloride with drugs metabolised by CYP2D6 (such as venlafaxine) might lead to increased levels of these drugs.

Medicinal products that inhibit CYP2D6, CYP1A2 and CYP 3A4 e.g., ketoconazole, cimetidine, quinidine, erythromycin and grapefruit juice might lead to increased levels of propafenone. When propafenone is administered with inhibitors of these enzymes, the patients should be closely monitored and the dose adjusted accordingly.

Combination therapy of amiodarone and propafenone hydrochloride 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.

Concomitant use of propafenone and phenobarbital and/or rifampicin (CYP3A4 inducers) may reduce the antiarrythmic efficacy of propafenone as a result of a reduction in propafenone plasma levels. Hence, response to propafenone hydrochloride therapy should be monitored during concomitant chronic phenobarbital and/or rifampicin treatment.

Special populations

Paediatric population

Interaction studies have only been performed in adults. It is not known whether the extent of interactions is similar in the paediatric age group to that in adults.

4.6. Pregnancy and Lactation

Pregnancy:
There are no adequate and well-controlled studies in pregnant women. Propafenone should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Propafenone 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.

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

4.7. Effects on Ability to Drive and Use Machines

Blurred vision, dizziness, fatigue and postural hypotension may affect the patient's speed of reaction and impair the individual's ability to operate machinery or motor vehicles.

4.8. Undesirable Effects

a. Summary of the safety profile

The most frequent and very common adverse reactions related to propafenone therapy are dizziness, cardiac conduction disorders and palpitations.

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with propafenone.

The reactions considered at least possibly related to propafenone are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed. The frequencies are based on clinical trial data from propafenone SR. It is expected that the adverse reactions and frequencies for IR formulations would be similar.

System Organ Class	**Very common ≥1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥1/1,000 to < 1/100**	**Not Known (cannot be estimated from the available data)**
Blood and lymphatic system disorders			Thrombocytopenia	Agranulocytosis Leukopenia Granulocytopenia
Immune system disorders				Hypersensitivity[1]
Metabolism and nutrition disorders			Decreased appetite	
Psychiatric disorders		Anxiety Sleep disorders	Nightmare	Confusional state
Nervous system disorders	Dizziness[2]	Headache Dysgeusia	Syncope Ataxia Paraesthesia	Convulsion Extrapyramidal symptoms Restlessness
Eye disorders		Vision blurred		
Ear and labyrinth			Vertigo	

disorders				
Cardiac disorders	Cardiac conduction disorders[3] Palpitations	Sinus bradycardia Bradycardia Tachycardia Atrial flutter	Ventricular tachycardia Arrythmia[4]	Ventricular fibrillation Cardiac failure[5] Heart rate reduced
Vascular disorders			Hypotension	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		Dyspnoea		
Gastrointestinal disorders		Abdominal pain Vomiting Nausea Diarrhoea Constipation Dry mouth	Abdominal distension Flatulence	Retching Gastrointestinal disturbance
Hepatobiliary disorders		Hepatic function abnormal[6]		Hepatocellular injury Cholestasis Hepatitis Jaundice
Skin and subcutaneous tissue disorders			Urticaria Pruritus Rash Erythema	Acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders				Lupus-like syndrome
Reproductive system and breast disorders			Erectile dysfunction	Sperm count decreased[7]
General disorders and administration site conditions		Chest pain Asthenia Fatigue Pyrexia		

[1] May be manifested by cholestasis, blood dyscrasias and rash
[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
[7] Decreased sperm count is reversible upon discontinuation of propafenone

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://sideeffects.health.gov.il

4.9. Overdose

Symptoms of overdosing:

Myocardial symptoms: The effects of propafenone 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 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, clonic-tonic 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. Attempts to achieve elimination via haemoperfusion are of limited efficacy. Owing to high protein binding (> 95%) and the large volume of distribution, haemodialysis is ineffective.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Antiarrhythmics, class IC

ATC-Code: C01BC03

Propafenone is a class IC anti-arrhythmic agent.

It has a stabilising action on myocardial membranes, reduces the fast inward current carried by sodium ions with a reduction in depolarisation rate and prolongs the impulse conduction time in the atrium, AV node and primarily, in the His-Purkinje system.

Impulse conduction through accessory pathways, as in WPW syndrome, is either inhibited, by prolongation of the refractory period or blockade of the conduction pathway, both in anterograde but mostly retrograde direction.

At the same time, spontaneous excitability is reduced by an increase of the myocardial stimulus threshold while electrical excitability of the myocardium is decreased by an increase of the ventricular fibrillation threshold.

Anti-arrhythmic effects: Slowing of upstroke velocity of the action potential, decrease of excitability, homogenisation of conduction rates, suppression of ectopic automaticity, lowered myocardial disposition to fibrillation.

Propafenone has moderate beta-sympatholytic activity without clinical relevance. However, the possibility exists that high daily doses (900 - 1200 mg) may trigger a sympatholytic (anti-adrenergic) effect.

In the ECG, propafenone causes a slight prolongation of P, PR and QRS intervals while the QT_C interval remains unaffected as a rule.

In digitalised patients with an ejection fraction of 35-50%, contractility of the left ventricle is slightly decreased. In patients with acute transmural infarction and heart failure, the intravenous administration of propafenone may markedly reduce the left ventricular ejection fraction but to an essentially lesser extent in patients in the acute stages of infarction without heart failure. In both cases, pulmonary arterial pressure is minimally raised. Peripheral arterial pressure does not show any significant changes. This demonstrates that propafenone does not exert an unfavourable effect on left ventricular function which would be of clinical relevance. A clinically-relevant reduction of left ventricular function is to be expected only in patients with pre-existing poor ventricular function.

Untreated heart failure might then deteriorate possibly resulting in decompensation.

5.2. Pharmacokinetic Properties

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

Absorption

Following oral administration, propafenone is nearly completely absorbed from the gastrointestinal tract in a dose-dependent manner. Maximal plasma concentrations are reached between two to three hours following the administration of propafenone hydrochloride. After a single dose of one tablet, bioavailability is about 50%. With repeated doses, plasma concentration and bioavailability rise disproportionately due to saturation of the first pass metabolism (CYP2D6) in the liver. 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 in the body. The steady-state volume of distribution is 1.9 to 3.0 L/kg. Therapeutic plasma levels are in the range of 150 ng/mL to 1500 ng/mL. The degree of plasma protein binding of propafenone is concentration dependent and decreased from 97.3% at 0.25 µg/mL to 81.3% at 100 µg/mL. In the therapeutic concentration range, more than 95% of propafenone is bound to plasma proteins.

Biotransformation and elimination

Comparing cumulative urinary excretion over 24 hours allowed for the calculation that 1.3% of intravenous (70 mg) and 0.65% of oral (600 mg) propafenone is excreted unchanged in the urine, i.e. propafenone is almost exclusively metabolised in the liver. The estimated propafenone elimination half-life ranges from 2 to 10 hours for extensive metabolisers and from 10 to 32 hours for poor metabolisers. A close positive correlation between plasma level and AV conduction time was seen in the majority of both healthy volunteers and patients. Clearance of propafenone is 0.67 to 0.81 L/h/kg.

After a plasma level of 500 ng/ml, the PR interval is statistically significantly prolonged as compared to baseline values which allows for dose titration and monitoring of the patients with the help of ECG readings. The frequency of ventricular extrasystoles decreases as plasma concentrations increase. Adequate anti-arrhythmic activity has, in single cases, been observed at plasma levels as low as <500 ng/ml.

Steady state is reached after 3 or 4 days, when bioavailability increases to about 100%. The recommended dosing regimen of propafenone is the same regardless of the metabolic status (i.e., poor or extensive metabolizers) for all patients.

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

Even in the presence of impaired renal function, reduced elimination of propafenone is not likely, which is confirmed by case reports and single kinetic studies in patients on chronic haemodialysis. However, accumulation of glucuronide metabolites was observed. Clinical chemistry values did not differ from those of patients with uncompromised kidneys. Propafenone hydrochloride should be administered cautiously in patients with renal disease.

Liver 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

None.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Excipients for Core: Microcrystalline Cellulose, Sodium Croscarmellose, Starch Pregelatinised, Hypromellose (substitution type 2910, viscosity 3 mPa•s), Magnesium Stearate, Purified Water.

Excipients for Film-Coating: Hypromellose (substitution type 2910, viscosity 3 mPa•s), Macrogol 6000, Titanium Dioxide (E 171), Macrogol 400, ,

6.2. Incompatibilities

None.

6.3. Shelf Life

The expiry date of the product is indicated on the packaging materials

6.4. Special Precautions for Storage

Store in a dry place below 30°C

6.5. Nature and Contents of Container

PVC/aluminium blister strips containing 30 or 50 or 100 tablets.

6.6. Instruction for Use/Handling

None.

7. LICENSE HOLDER

ABBOTT MEDICAL LABORATORIES LTD, ISRAEL
KIRIAT ATIDIM, POB 58099, TEL-AVIV 61580, ISRAEL

8. REGISTRATION NUMBER

103-99-27103-00

Revised on May 2022

תאריך עדכון עלון	פרקים שהתעדכנו	אסמכתא לעדכון עלון	הערות
05-2022	אימוץ עלון כלשונו – מעבר לפורמט עדכני של עלון לרופא התואם לפורמט של EMA	UK -SmPC-Arythmol 150mg-03.2021	
10-2015	שינוי שם תכשיר, שינוי בעל רישום, שינוי שם יצרן		
03-2014		UK- 11.2012	