Rytmonorm® 150 mg

1. NAME OF THE MEDICINAL PRODUCT
Rytmonorm® tablet 150mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One Rytmonorm® tablet 150 mg contains 150 mg propafenone hydrochloride.

3. PHARMACEUTICAL FORM
White to off white film coated tablets, biconvex.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Symptomatic supraventricular tachyarrhythmias warranting treatment, such as AV junctional tachycardias, supraventricular tachycardias in patients with WPW syndrome or paroxysmal atrial fibrillation. Serious symptomatic ventricular tachyarrhythmias if life-threatening or necessitating treatment in the judgement of the physician.

4.2. Posology and method of administration
The individual maintenance dose should be determined under cardiological surveillance including ECG monitoring and repeated blood pressure control (stabilization phase) unless otherwise prescribed by the physician.

For initial and maintenance treatment a daily dose of 450-600 mg divided in two or three doses per day (one 150 mg Rytmonorm coated tablet three times daily) is recommended. Occasionally an increase of the daily dose to 900 mg may be necessary (two 150 mg Rytmonorm coated tablets three times daily).

These data apply to patients with a body weight of about 70 kg. The daily doses 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 three to four days.
This daily dose should be exceeded only in exceptional circumstances and under strict cardiological control.

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

Particularly in the elderly and in patients with marked previous myocardial damage (relevant impairment of left ventricular function or structural myocardial disease), the first dose increase should take place after 5 to 8 days of therapy.

When prescribing propafenone, it should be taken into account that there is no evidence that antiarrhythmic treatment with Class 1 antiarrhythmics improves survival.

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

Liver/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.
Propafenone hydrochloride should be administered cautiously in patients with renal disease.

The dosage must be adjusted in patients with liver disease.

Method of administration
Because of the bitter taste and the surface anaesthetic action of propafenone, the coated tablets should be swallowed whole together with some liquid.

4.3. Contraindications
- Known hypersensitivity to propafenone hydrochloride or to any of the excipients
- Known Brugada Syndrome (see **Special warnings and precautions for use**)
- Incident of myocardial infarction within the last 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
  - 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
- Manifest electrolyte imbalance (e.g. potassium metabolism disorders)
- Severe obstructive pulmonary disease
- Myasthenia gravis
- Concomitant treatment with ritonavir

4.4. Special warnings and precautions for use
Propafenone like other antiarrhythmics may cause proarrhythmic effects, i.e. it may cause new or worsen preexisting arrhythmias (see 4.8). It is essential that each patient given propafenone hydrochloride be evaluated electrocardiographically and clinically prior to and during therapy to determine whether the response to propafenone hydrochloride supports continued treatment.

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, an ECG should be performed to rule out changes suggestive of Brugada syndrome.

Propafenone hydrochloride treatment may affect both the pacing and sensing thresholds of artificial pacemakers. Pacemaker function should therefore be checked and, if necessary, reprogrammed.

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

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

Propafenone hydrochloride should be used with caution in patients with obstruction of the airways, e.g. asthma.

4.5. Interactions with other medicinal products and other forms of interactions
A possible potentiation of drug side effects may occur when propafenone hydrochloride is taken in conjunction with local anesthetics (eg. pacemaker implantation, surgery or dental work) and other drugs which have an inhibitory effect on the heart rate and/or myocardinal contractility (eg. beta block-ers, tricyclic antidepressants).

Coadministration of propafenone hydrochloride 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 propafenone hydrochloride therapy.

Drugs that inhibit CYP2D6, CYP1A2 and CYP3A4, eg. ketoconazole, cimetidine, 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.

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

Combination therapy of amiodarone and propafenone hydrochloride can affect conduction and repolarization 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 propafenone or lidocaine have been seen following their concomitant use in patients. However, concomitant use of propafenone hydrochloride and intravenous lidocaine have been reported to increase the risks of central nervous system side effects of lidocaine.

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

Concomitant use of propafenone hydrochloride and rifampicin may reduce the antiarrhythmic efficacy of propafenone hydrochloride as the result of a reduction in the propafenone plasma levels. Close monitoring of the clotting status in patients receiving concomitant oral anticoagulants (eg.phenprocoumon warfarin) is recommended as propafenone hydrochloride may enhance the efficacy of these drugs resulting in an increased prothrombin time.

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

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

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 hydrochloride 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 and motor vehicles.

4.8. Undesirable effects
Reactions from Clinical Trials or Postmarketing Surveillance
The clinical adverse events that occurred in at least one of the 885 patients receiving propafenone hydrochloride sustained release (SR) in five phase II studies and two phase III studies are shown in Table 1. It is expected that the adverse reactions and frequencies for immediate release (IR) formulations would be similar. This table also includes adverse reactions 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 (≥ 1/1000 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.

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				Hypersensitivity[1]

disorders				
Metabolism and nutrition disorders			Decreased appetite	
Psychiatric disorders		Anxiety Sleep disorders	Nightmare	Confusional state
Nervous system disorders	Dizziness[2]	Headache, dysgeusia	Syncope, Ataxia, Paresthesia	Convulsion Extrapyramidal symptoms Restlessness
Eye disorders		Vision blurred		
Ear and labyrinth disorders			Vertigo	
Cardiac disorders	Cardiac conduction disorders[3], palpitations	Sinus bradycardia, Bradycardia, Tachycardia, Atrial flutter	Ventricular tachycardia, Arrhythmia[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 (AGEP)
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 whjch manifest as an increase in heart rate (tachycardia) or ventricular fibrillation. Some of these arrhythmias can be life-threatening and may require resuscitationto 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.

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 automatically, 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, clonic-tonic convulsions, paraesthesia, somnolence, coma and respiratory arrest may occur.

Treatment

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

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antiarrhythmics, class 1C
ATC-Code: C01 BC 03

Propafenone hydrochloride is a class 1c antiarrhythmic drug with some structural similarities to beta-blocking agents.

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.

5.2. Pharmacokinetic properties

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

Absorption
Maximal plasma concentrations are reached between two to three hours following the administration of propafenone hydrochloride. 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. 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 µg/mL to 81.3% at 100 µg/mL.

Biotransformation and elimination
There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from two to ten hours (i.e. extensive metabolizers). These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed (i.e., poor metabolizers). Slow metabolizers had higher propafenone plasma concentrations which they required for suppression of arrhythmia since they did not produce the active metabolite 5-hydroxypropafenone (5-OHP). These higher propafenone plasma concentrations may lead to clinically evident beta-blockade. The estimated propafenone elimination half-life ranges from two to ten hours for extensive metabolizers and from ten to 32 hours for poor metabolizers. Clearance of propafenone is 0.67 to 0.81 L/h/kg.

Because steady state is reached after three to four days of dosing of propafenone hydrochloride, the recommended dosing regimen of propafenone is the same regardless of the metabolic status (i.e., poor or extensive metabolizers) for all patients.

Linearity/non-linearity
In extensive metabolizers, the saturable hydroxylation pathway (CYP2D6) results in nonlinear pharmacokinetics. In slow metabolizers, propafenone pharmacokinetics are linear.

Inter/intra subject 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.

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.

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. Pre-clinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose
Sodium Croscarmellose
Maize starch
Hypromellose
Magnesium stearate
Purified water
Macrogol 400
Macrogol 6000
Titanium Dioxide

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
Please refer to carton for expiry.

6.4. Special precautions for storage
Store at or below 30°C.

6.5. Pack size
Box of 50 tablets.

7. NAME AND ADDRESS OF PRODUCT OWNER

Abbott Products Operations AG
Hegenheimermattweg 127
4123 Allschwil
Switzerland

8. DATE OF REVISION

25 May 2022 (SIN-PROA-0522/0)