RYTMONORM®

PROPAFENONE HYDROCHLORIDE

NAME OF THE MEDICINAL PRODUCT

Rytmonorm® 150 mg, Rytmonorm® 300 mg

COMPOSITION OF THE MEDICINAL PRODUCT

Rytmonorm 150 mg:
1 film-coated tablet contains 150 mg of propafenone hydrochloride.

Rytmonorm 300 mg:
1 film-coated tablet contains 300 mg of propafenone hydrochloride.

DOSAGE FORM

Film-coated tablets

CLINICAL PARTICULARS

Therapeutic indications

Symptomatic supraventricular tachyarrhythmias requiring treatment, such as AV junctional tachycardia, supraventricular tachycardia in patients with WPW syndrome or paroxysmal atrial fibrillation.

Severe symptomatic ventricular tachyarrhythmias, if the physician considers these to be life-threatening.

Posology and method of administration

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. Regular check-ups are necessary during treatment (e.g. standard ECG at monthly intervals, Holter monitoring at 3-monthly intervals, exercise ECG, if appropriate). An adjustment in treatment should be considered if there are changes in the ECG 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.

The dosage is to be adjusted to the individual patient's requirements. The following doses are recommended: In the titration phase and for maintenance therapy in patients weighing around 70 kg, a daily dose of 450 – 600 mg of propafenone hydrochloride is recommended, i.e. 150 mg of propafenone hydrochloride 3 times daily to 300 mg of propafenone hydrochloride twice daily. Occasionally it may be necessary to increase the daily dose to 300 mg of propafenone three times daily. The daily doses should be reduced accordingly in patients with a lower body weight. Dose increases should not be attempted until the patient has been receiving treatment for 3 to 4 days. The individual maintenance dose should be determined under repeated ECG monitoring and blood pressure control (titration phase). The dosage should be reduced if there is significant widening of the QRS complex or 2nd or 3rd degree AV block. The film-coated tablets should be taken whole with sufficient liquid (e.g. a glass of water), without being sucked or chewed, after meals. The duration of treatment is to be determined by the attending physician.

Contraindications

Rytmonorm may not be taken in cases of:

- known hypersensitivity (allergy) to the active ingredient, propafenone hydrochloride, or to any of the other ingredients of Rytmonorm.
- overt heart failure
- cardiogenic shock, unless this is caused by arrhythmia
- severe symptomatic bradycardia
- within three months of myocardial infarction or where cardiac output is impaired (left ventricular output is less than 35%), except for patients suffering from life-threatening ventricular arrhythmia
- severe impulse conduction disorders (such as, 2nd or 3rd degree SA or AV block, bundle branch block (without pacemaker implantation))
- sick sinus syndrome (without pacemaker implantation)
- severe hypotension
- manifest electrolyte imbalance (e.g. potassium metabolism disorders)
- severe obstructive airways disease
- myasthenia gravis
- concomitant administration of 800 – 1200 mg of ritonavir/day.

Special warnings and precautions for use

Owing to their high active ingredient content, film-coated tablets containing 150 mg and 300 mg of propafenone hydrochloride are, as a rule, not suitable for use in children. In elderly patients or patients suffering from severe heart damage, the dosage should be titrated very gradually and with great care. When treating paroxysmal atrial tachycardia, a 2:1 or 1:1 transfer to the ventricle and resulting very rapid ventricular rate (e.g. > 180 beats per minute) may occur as the atrial fibrillation converts to atrial flutter. In patients with pacemakers, the pacing and sensing threshold may change while on propafenone hydrochloride treatment. Pacemaker function should therefore be checked and, if necessary, re-programmed. As is the case with other class 1c antiarrhythmic agents, patients with severe structural heart disease may experience serious adverse reactions while receiving propafenone hydrochloride treatment. When prescribing propafenone, it should be taken into account that there is no evidence of antiarrhythmic treatment with Class I antiarrhythmics improving survival.

Interactions with other medicinal products and other forms of interaction

The following interactions with this medicinal product must be kept in mind:

A possible potentiation of drug efficacy must be taken into consideration 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 heart rate and/or myocardial contractility (e.g. beta blockers, tricyclic antidepressants).
Increases in propranolol, metoprolol, desipramine, ciclosporin and digoxin plasma or blood levels have been reported during propafenone hydrochloride therapy. This may enhance the efficacy of the above-mentioned drugs. In one case, theophylline plasma concentrations doubled when propafenone was given concomitantly. If symptoms of overdosage are observed, the plasma concentrations should be determined and the doses reduced, as appropriate.

Concomitant administration of cimetidine, quinidine, ketoconazole, erythromycin (drug products that inhibit the cytochrome P 450 isoenzymes CYP2D6, CYP1A2 and CYP3A4), grapefruit juice and propafenone hydrochloride may enhance propafenone hydrochloride efficacy (owing to an increase in propafenone hydrochloride plasma concentrations).

When using propafenone hydrochloride and drug products that are metabolised via the isoenzyme CYP2D6 (such as venlafaxin), the plasma concentration of these medications may be increased.
Concomitant use of propafenone hydrochloride and phenobarbital and/or rifampicin may reduce the antiarrhythmic efficacy of propafenone hydrochloride. This is due to a reduction in the propafenone hydrochloride plasma levels.

Concomitant use of amiodarone and propafenone hydrochloride may affect impulse conduction and repolarisation in the heart and lead to rhythm disorders with the risk of provoking proarrhythmias. A dose adjustment of both drug products may be required depending on the therapeutic effect.

No significant changes in the pharmacokinetics of propafenone hydrochloride and lidocaine were observed on concomitant administration of these two drug products. However, an increased risk of lidocaine-related central nervous side effects has been reported on concomitant use of propafenone hydrochloride and intravenous lidocaine.

Phenobarbital is known to induce the CYP3A4 isoenzyme. Propafenone hydrochloride treatment should be monitored during concomitant long-term use of phenobarbital.

When propafenone hydrochloride and fluoxetin are administered simultaneously in patients who are extensive metabolisers, the C_{max} and AUC for S-propafenone (the levorotatory enantiomer) are increased by 39 % and 50 %, respectively, while the C_{max} and AUC for R-propafenone (the dextrorotatory enantiomer) are increased by 71 % and 50 %, respectively. Propafenone hydrochloride plasma concentrations may be increased when propafenone hydrochloride and paroxetin are taken simultaneously. Lower doses of propafenone hydrochloride may suffice to achieve the desired therapeutic efficacy.

Close monitoring of the clotting status is recommended in patients receiving concomitant oral anticoagulants (e.g. phenprocoumon, warfarin) as propafenone increases the plasma levels of these drugs thereby increasing prothrombin time. The dosage of these drugs should be adjusted, if necessary.

Pregnancy and lactation

There is inadequate experience in the use of Rytmonorm in pregnant and breast-feeding women. In the few cases that are known, no complications occurred during pregnancy and lactation and the neonates were normal from a clinical point of view. Animal studies have not revealed any pre- or perinatal damage in the offspring after clinically relevant doses. However, as propafenone is passed on to the unborn child and is excreted in breast milk, the benefit of treatment during pregnancy or lactation has to be weighed against the potential risks for the child.

Effects on ability to drive and use machines

Even when taken as prescribed, this drug may affect the individual's ability to drive a vehicle, operate machinery or work safely under precarious conditions. This applies particularly at the beginning of treatment, on increasing the dose or when switching to another medication as well as when alcohol is consumed simultaneously.

Undesirable effects

The following undesirable effects may occur during Rytmonorm treatment.

The classification of side effects is based on their rate of incidence as listed below:

Very common:	> 10%
Common:	> 1% - <10%
Uncommon:	> 0.1% - <1%
Rare:	> 0.001% - < 0.1%
Very rare:	< 0.01% or unknown

Cardiovascular system

Common: Circulatory disorders with a tendency to postural hypotension in patients assuming an upright position or after standing over extended periods of time (orthostatic hypotension) may occur, particularly in elderly patients with impaired myocardial function. Dizziness, syncope, chest pain. Proarrhythmic effects which alter or exacerbate cardiac arrhythmias; these can lead to interference with the heart action and possible cardiac arrest. These proarrhythmic effects manifest either as bradycardia, conduction disorders (i.e. sinoatrial, atrioventricular or intraventricular block) or as an increase in heart rate (i.e. new onset of ventricular tachycardia). Heart failure may be exacerbated.
Rare: Ventricular flutter or fibrillation.

Gastrointestinal tract

Common: Gastrointestinal disorders (e.g. loss of appetite, nausea, retching, bloating, constipation, abdominal pain), dry mouth, bitter taste and numbness in the mouth, particularly when higher initial doses are administered.

Liver and gall bladder

Uncommon: Cholestasis as a symptom of a hyperergic-allergic reaction and/or liver function disorders (increase in liver-specific enzymes such as serum transaminases, alkaline phosphatase), jaundice and hepatitis.

Breast and reproductive organs

Rare: Loss of potency and drop in semen count (after high doses of propafenone hydrochloride) which are reversible on discontinuation of the medication. Since treatment with propafenone hydrochloride may be vital to the patient's health, the medication may not be discontinued without first consulting a physician.

Respiratory System

Uncommon: Respiratory distress in patients susceptible to bronchospasm.

Skin and mucosa (allergic reactions)

Uncommon: Allergic skin reactions (e.g. reddening, itching, exanthema, urticaria).
Rare: Increase in antinuclear antibody count, lupus-like syndrome.

Haemic and lymphatic system

Rare: Leukocytopenia and/or granulocytopenia or thrombocytopenia, all of which are reversible on discontinuation of propafenone hydrochloride. Agranulocytosis.

Psychological

Common: Anorexia
Uncommon: Fatigue, psychological disorders such as anxiety and confusion, restlessness, nightmares and sleep disorders.

Eyes

Common: Blurred vision

Nervous System

Common: Paraesthesia
Uncommon: Extrapyramidal symptoms, ataxia
Very rare: Convulsions on overdosage.

General

Common: Fever
Uncommon: Headache.

Overdose
Symptoms:
Myocardial symptoms
The toxic effects of propafenone hydrochloride 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 and ventricular fibrillation. Furthermore, reduction in contractility (negative inotropic effect) may cause hypotension which, in severe cases, can lead to cardiovascular shock.

Non-cardiac symptoms
Headache, dizziness, blurred vision, paraesthesia, tremor, nausea, constipation and dry mouth may occur frequently. In severe cases of poisoning, clonic-tonic convulsions, paraesthesia, somnolence, coma and respiratory arrest may occur. Overdosage can result in death.

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

Specific measures:
Bradycardia:
Reduction of the dose or discontinuation of the drug; atropine, if appropriate.
SA block and 2nd or 3rd degree AV block:
-Atropine
-Pacemaker therapy, if appropriate
-Intraventricular heart block (bundle branch block)

Reduction of the dose or discontinuation of the drug. Electrocardioversion, if needed, as no safe antidote to bundle branch block induced by class 1 antiarrhythmic agents is available. If electrostimulation is not viable, an attempt should be made to shorten the QRS interval by administering high doses of orciprenaline.

Heart failure accompanied by a drop in blood pressure:
-Discontinuation of the drug
-Cardiac glycosides

High-dosed nitroglycerine in the event of pulmonary oedema, diuretics, if necessary, catecholamines (e.g. adrenaline and/or dopamine and dobutamine).

Measures to be taken in cases of acute overdosage (e.g. attempted suicide):
-In the event of severe hypotension and bradycardia (in general the patient is unconscious): Atropine 0.5-1 mg i.v., adrenaline 0.5-1 mg i.v. or , if necessary, adrenaline by continuous drip infusion. The rate will depend on the clinical response.
-In the event of cerebral convulsions: Intravenous diazepam. Airways must be kept patent. Intubation, if called for, and controlled respiration (relaxation, e.g. 2-6 mg Pancuronium).

Circulatory arrest caused by asystole or ventricular fibrillation:
-Basic cardiopulmonary resuscitation measures (ABC rule): Airways, i.e. free airways and/or intubate. Breathing, i.e. increase oxygen supply, if possible. Circulation, i.e. heart massage (for several hours, if necessary!)
-Adrenaline 0.5-1 mg i.v. or 1.5 mg diluted in 10 ml physiological saline solution via tracheal tube. Repeat as needed depending on clinical response.
-Sodium bicarbonate 8.4%, initially 1 ml/kg i.v., repeat after 15 minutes. Defibrillate in the event of ventricular fibrillation. If there is resistance to therapy, repeat after having given 5-15 mval of potassium chloride solution intravenously.
-Infusion with added catecholamines (adrenaline and/or dopamine/dobutamine).
-If needed, infusion with added sodium chloride solution (80-100 mval) until a serum sodium level of 145-150 mval/l is reached.

Gastric lavage
Dexamethasone 25-50 mg i.v.
Sorbitol solution 40% 1 ml/kg body weight i.v.
Pacemaker.

Symptomatic intensive care measures.

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.

Pharmacological properties

Pharmacodynamic properties

Propafenone hydrochloride is an antiarrhythmic agent with membrane-stabilizing, sodium channel blocking properties (Vaughan Williams, class 1c). It also possesses beta-adrenergic agonistic 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, AV node and ventricles are prolonged. Propafenone hydrochloride prolongs the refractory periods in the accessory pathways in patients with Wolff-Parkinson-White syndrome (WPW syndrome).

Pharmacokinetic properties

Peak plasma concentrations of propafenone hydrochloride are reached 2 to 3 hours after oral dosing. Propafenone hydrochloride is subject to extensive presystemic biotransformation marked by saturation (CYP2D6 hepatic first pass metabolism), its absolute bioavailability being dependent on the dose and route of administration. There are two genetically dependent metabolic patterns for propafenone hydrochloride. In more than 90 % of patients, propafenone hydrochloride is rapidly and "extensively" metabolised with an elimination half-life of 2 to 10 hours. These patients metabolise propafenone hydrochloride into two active metabolites: 5-hydroxy-propafenone (norpropafenone) formed via CYP3A4 and CYP1A2. In less than 10% of the patients, propafenone hydrochloride is metabolised at a slower rate since the 5-hydroxy metabolite is only formed to a minimal extent or not at all. The estimated elimination half-life for propafenone hydrochloride after oral dosing is 2.8 to 11 hours for patients who are "extensive" metabolisers", and approximately 17 hours for patients who are poor metabolisers. Owing to the saturable hydroxylation step (CYP2D6), "extensive" metabolisers display non-linear pharmacokinetics whereas poor metabolisers display linear pharmacokinetics. Since steady state is reached after 3 to 4 days, the dosage regime is the same for all patients receiving propafenone hydrochloride orally. The considerable range of individual variability in the pharmacokinetics of propafenone hydrochloride, owing primarily to the hepatic first-pass effect and non-linear pharmacokinetics in "extensive" metabolisers, must be taken into account. The considerable variability in plasma levels requires that dose titration in patients be undertaken with particular care and under close clinical and electrocardiographic monitoring for signs of toxicity. Therapeutic plasma concentrations lie between 100-1500 ng/ml. Propafenone hydrochloride is known to pass the placental barrier in humans and is excreted in breast milk. Foetal transfer: In one reported case, the concentration of propafenone hydrochloride in the umbilical cord amounted to about 30 % of that in the maternal blood. Excretion in breast milk: in one reported case, the concentration of propafenone hydrochloride in the breast milk was between 4% and 9 % of that in the maternal blood.

Pharmaceutical particulars

Incompatibilities
None known to date

Special instructions for storage

Do not store above 25° C.

Nature and contents of container

Rytmonorm 150 mg:			
Original pack tablets	containing	20	film-coated
Original pack tablets	containing	50	film-coated
Original pack tablets	containing	100	film-coated
Rytmonorm 300 mg:			
Original pack tablets	containing	20	film-coated
Original pack tablets	containing	50	film-coated
Original pack tablets	containing	100	film-coated

Date of revision of the text

July 2007

THIS IS A MEDICAMENT

- Medicament is a product, which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

KEEP ALL MEDICAMENTS OUT OF REACH OF CHILDRENS

Council of Arab Health Ministers
Union of Arab Pharmacists

إن هذا دواء

- لدوء مستحضر يؤثر على صحتك، وإستهلاكه خلافاً للتعليم ت يعر ضك للخطر.
- إتبع بدقة وحفة لطبيب وطريقة لإستعم ل لمنصوص عليه وتعليم ت لصيدلي لذي صرفه لك.
- لطبيب و لصيدلي هم لخبير ن في لدوء وفي نفعه وضرره.
- لا تقطع مدة لعلاج لمحددة لك من تلق ء نفسك.
- لا تكرر صرف لدوء بدون وصفة طبية.

لا تترك الأدوية في متناول أيدي الأطفال.

مجلس وزراء الصحه العرب
واتحاد الصيادلة العرب

AI Affiliate Print Approval
Reviewed and approved by: Signature Date
Name in block letters:

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