Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Arythmol 150 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg propafenone hydrochloride.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.
Product imported from the UK:
White, biconvex, film-coated tablets and embossed “150” on one face.

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 tablets should be swallowed whole and taken with a drink after food.
The dosage should be adjusted to the individual patient’s requirements.
In those patients in whom significant widening of the QRS complex or second or third AV block occurs, a dose reduction should be considered.

Adults: A daily doses of 450 to 600 mg of propafenone hydrochloride, divided in two or three doses per day, is recommended in the titrated period and for maintenance therapy in patients weighing around 70 kilograms. 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 is receiving treatment for three to four days.

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

Elderly: In elderly patients or patients with relevant impairment of ventricular function (left ventricular ejection fraction less than 35%) or structural myocardial disease, treatment should applies to maintenance therapy. Any dose increases that may be required should not be undertaken until after five to eight days of therapy.
In patients whose liver and /or kidney function is impaired, there may be drug accumulation after the standard therapeutic doses. Nonetheless, patients with these conditions can still be titrated on propafenone hydrochloride under ECG and plasma level monitoring.

Arythmol tablets are not recommended for use in children.

4.3 Contraindications

Known hypersensitivity to propafenone or to any of the other ingredients.

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.
Manifest electrolyte imbalance (e.g. potassium metabolism disorders).
Severe obstructive pulmonary disease.

4.4 Special warnings and precautions for use

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

Propafenone hydrochloride IR may worsen myasthenia gravis.

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 potential for conversion of paroxysmal atrial fibrillation to atrial flutter with accompanying 2:1 or 1:1 conduction block. As with other class 1C anti-arrhythmic agents, patients with significant structural heart disease may be predisposed to serious adverse effects.

Because of the beta-blocker effect, care should be taken in the treatment of patients with asthma.

4.5 Interaction with other medicinal products and other forms of interaction

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

Co-administration of propafenone hydrochloride with drugs metabolised by CYP2D6 (such as venlafaxine) might lead to increased levels of these drugs. Increase in propranolol,
metoprolol, desipramine, cyclosporin, theophylline and digoxin plasma levels or blood levels have been reported during propafenone hydrochloride therapy.

Drugs that inhibit CYP2D6, CYP1A2 and CYP3A4 e.g. 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 800-1200 mg/ day doses of ritonavir and propafenone hydrochloride is contraindicated.

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.

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

Phenobarbital is a known inducer of CYP3A4. Response to propafenone hydrochloride

Concomitant use of propafenone hydrochloride and rifampicin may reduce the anti-arrhythmic efficacy of propafenone hydrochloride as the result of a reduction in the propafenone plasma levels.

Close monitoring of the clotting status in patients receiving oral anti-coagulants (e.g. Phenoprocoumon, warfarin) is recommended as propafenone hydrochloride may enhance the efficacy of the drugs resulting in an increased prothrombin time.

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

Caution should be taken with regards to digitalis toxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy
Propafenone hydrochloride IR should be used 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 concentrations of propafenone in the umbilical cord have been reported to be about 30% of that of the maternal blood.

Animal studies have not shown any teratogenic effects, but there is no experience of the use of the drug in human pregnancy.

Lactation
Excretion of propafenone in breast milk has not been studied. Limited data suggests that propafenone may be excreted in 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 or motor vehicles.

4.8 Undesirable effects

The following adverse events have been reported with this or other formulations of propafenone hydrochloride. A cause and effect relationship may not have been established.

Body System	**Preferred Term**
Blood and lymphatic system disorders	Isolated case of leukocytopenia and/ or granulocytopenia or thrombocytopenia; agranulocytosis have been reported.
Immune system disorders	Allergic reactions.
Metabolism and nutritional disorders	Anorexia.
Psychiatric disorders	Anxiety, confusion can occur rarely.
Nervous system disorders	Dizziness, headache, syncope, ataxia and paresthesia. Very rarely, restlessness, nightmares, sleep disorders and extrapyramidal symptoms may occur. Vertigo may occur occasionally.

Eye disorders	Blurred vision may occur occasionally after a high initial dose.
Cardiac disorders	A marked reduction in heart rate (bradycardia) or conduction disorders (i.e. atrioventricular or interventricular block) may occur very rarely. Occasionally proarrhythmic effects which manifest as an increase in heart rate (tachycardia), or ventricular fibrillation may also occur.
Vascular disorders	Hypotension, including postural hypotension and orthostatic hypotension can be seen occasionally.
Gastrointestinal disorders	Occasionally, especially with high initial doses, nausea, vomiting, constipation, dry mouth, bitter taste, abdominal pain can occur.
Hepatobiliary disorders	Rarely, liver abnormalities, including hepatocellular injury, cholestasis, jaundice and hepatitis may occur due to the individuals hypersensitivity of the hyperergic-allergic type.
Skin and subcutaneous tissue disorders	Rarely, allergic reaction such as reddening of the skin, rash, itching, urticaria may occur.
Musculoskeletal and connective tissue disorders	Isolated case of lupus syndrome have been reported, these are reversible on discontinuation of the medicine.
Reproductive system and breast disorders	Impotence, in some cases, a diminution of potency and a drop in sperm count have been observed after high doses of Arythmol. This phenomenon is reversible when treatment is discontinued. However, since treatment with Arythmol is vital, the drug must not be discontinued without consulting your doctor.
General disorders and administration site conditions	Rarely fatigue can occur. Chest pain. Convulsions following an overdose have been reported very, very rarely. Bronchial spasms may rarely occur on predisposed patients.
Investigations	Elevated liver enzymes (serum transaminases and alkaline phosphatases).

4.9 Overdose

Symptoms
Myocardial symptoms
Experience with overdosage is limited. No specific antidote is known. Procedures to enhance drug elimination from the body by haemodialysis or haemoperfusion are unlikely to succeed because of the large volume of drug distribution. 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 and ventricular fibrillation. Hypotension may also occur. Convulsions, somnolence and death may occur. The usual emergency measures for acute cardiovascular collapse should be applied. In severe conduction disturbance associated with compromised cardiac function, atropine, isoprenaline or pacemaker therapy may be required. If electrical stimulation is not possible, an attempt should be made to shorten the QRS duration and increase the heart rate with high doses of isoprenaline. Bundle branch block by itself is not an indication for isoprenaline. Hypotension may require inotropic support. Convulsions should be treated with i.v. diazepam.

Non –cardiac symptoms
Convulsions, somnolence and death may occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Propafenone hydrochloride is an antiarrhythmic agent with a membrane stabilising, 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 the rise of the action potential thereby slowing down the 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 on patients with WPW syndrome.

5.2 Pharmacokinetic properties

Maximal plasma concentrations are reached between two and three hours following the administration of propafenone hydrochloride IR. Propafenone is known to undergo extensive and saturable pre-systemic biotransformation (CYP2D6 hepatic first pass effect) which results in a dose- and dosage- form-dependant absolute bioavailability.

There are two genetically determined patterns of propafenone hydrochloride metabolism. In over 90% of patients, the drug is rapidly and extensively metabolised with an elimination half-life from two to ten hours. These patients metabolise propafenone into two metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both 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. The estimated propafenone IR elimination half-life ranges from 2.8 to 11 hours for extensive metabolisers and is around 17 hours for poor metabolisers.
In extensive metabolisers, the saturable hydroxylation pathway (CYP2D6) results in nonlinear pharmacokinetics. In slow metabolisers, propafenone pharmacokinetics are linear.

Because the steady state is reached after three to four days of dosing in all patients, the recommended dosing regimen of propafenone hydrochloride IR is the same for all patients.

With Arythmol, 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 metabolisers. 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.

Renal impairment
Propafenone hydrochloride should be administered cautiously in patients with renal disease.

Hepatic impairment
The dosage must be adjusted in patients with liver disease.

5.3 Preclinical safety data

Intravenous administration of propafenone at doses within the toxic range has caused reversible disorders of spermatogenesis at irregular intervals in monkeys, dogs and rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Maize starch
Croscarmellose sodium
Hypromellose
Magnesium stearate
Hypromellose

Macrogol 400
Macrogol 6000
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister strips of 15 tablets contained in an overlabelled outer carton.
Pack size: 90 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT