SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Propafenone hydrochloride 300mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300mg propafenone hydrochloride
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet

White to off-white, round, biconvex, film-coated tablets, with score line on one side and plain on the other side.

The tablet can be divided in to equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Propafenone is indicated for the prophylaxis and treatment of ventricular arrhythmias.

Propafenone is also indicated for the prophylaxis and treatment of paroxysmal supraventricular tachyarrhythmias which include paroxysmal atrial flutter/fibrillation and paroxysmal re-entrant tachycardia's involving the AV node or accessory bypass tracts, when standard therapy has failed or is contraindicated.

4.2 Posology and method of administration

It is recommended that propafenone therapy should be initiated under hospital conditions, by a physician experienced in the treatment of arrhythmias. The individual maintenance dose should be determined under cardiological surveillance including ECG monitoring and blood pressure control. If the QRS interval is prolonged by more than 160msec or the PQ interval is prolonged by more than 20%, the dose should be reduced or discontinued until the ECG returns to normal limits.

Adults

Initially, 150 mg three times daily increasing at a minimum of three-day intervals to 300 mg twice daily and if necessary, to a maximum of 300 mg three times daily.

The tablets should be swallowed whole and taken with a drink after food. A reduction in the total daily dose is recommended for patients below 70 kg bodyweight.

Elderly

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. Treatment should be initiated gradually and with particular caution in small incremental doses. 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.

Children

A suitable dosage form of propafenone hydrochloride tablets for children is not available.

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 plasma level monitoring.

4.3 Contraindications

- Hypersensitivity to the propafenone or to any of the excipients listed in section 6.1
- 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. hyperkalemia or other potassium metabolism disorders), severe obstructive pulmonary disease or severe hypotension.
- Propafenone may worsen myasthenia gravis.
- Patients with known Brugada Syndrome.

Unless patients are adequately paced (see section 4.4, Special Warnings and Precautions for Use), propafenone 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 in the absence of an artificial pacemaker.

Minor prolongation of the PR interval and intra-ventricular conduction defects (QRS duration of less than 20%) are to be expected during treatment with propafenone and do not warrant dose reduction or drug withdrawal.

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

4.4 Special warnings and precautions for use

Electrolyte disturbances should first be treated before treatment with propafenone.

The weak negative inotropic effect of propafenone may assume importance in patients predisposed to cardiac failure. In common with other anti-arrhythmic drugs, propafenone 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 or asthma.

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

There is a risk of pro-arrhythmic effects, as with other anti-arrhythmics. Worsening of the ventricular arrhythmias is possible.

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.

For the treatment of ventricular arrhythmias, the patient should be under cardiological surveillance including ECG monitoring and blood pressure control and defribillator facilities should be available.

Treatment stop should be considered with one of the following ECG-changes:

- QRS or QT-interval prolongation with more than 25%,
- PR-interval prolongation with more than 50%,
- QT-interval prolongation with more than 500 msec,
- or a increase in numbers or worsening of the arrhythmias

Propafenone like other antiarrhythmics may cause proarrhythmic effects, i.e., it may cause new or worsen pre-existing arrhythmias (see section 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.

Excipients

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

4.5 Interaction with other medicinal products 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 intravenous 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 Cmax and AUC by 39 and 50% and the R-propafenone Cmax 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.

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

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 Fertility, 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 disorders			Vertigo	
Cardiac disorders	Cardiac conduction disorders[3] Palpitations	Sinus bradycardia Bradycardia Tachycardia	Ventricular tachycardia Arrythmia[4]	Ventricular fibrillation Cardiac failure[5] Heart rate reduced

		Atrial flutter		
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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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

ATC code for propafenone is C01B C03.

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 QTC 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

Core

Maize starch

Hypromellose E5

Microcrystalline cellulose

Croscarmellose sodium

Magnesium stearate

Film-coat

Talc

Hypromellose E5

Titanium dioxide

Macrogol 6000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original carton to protect from moisture.

6.5 Nature and contents of container

Tablets are packed in Aluminium//PVC/PVdC blisters containing 20, 50, 60 & 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0356

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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