Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Arythmol SR 425 mg prolonged release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release capsule contains 425 mg, propafenone hydrochloride

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard.

White to almost opaque capsule stamped with red Abbott logo and “425” on the cap.and three red stripes on the body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Arythmol SR (sustained/prolonged release) is indicated to prolong the time to recurrence of symptomatic atrial arrhythmias in patients without significant structural heart disease and with a history of symptomatic atrial fibrillation.

4.2 Posology and method of administration

The dose of Arythmol SR must be individually titrated on the basis of response and tolerance. Titration to the individual maintenance dose should be supervised by a cardiologist (repeated ECG recordings and blood pressure measurements). It is recommended that therapy be initiated with 225 mg propafenone hydrochloride (as prolonged-release capsules) given every twelve hours. The dosage may be increased at a minimum interval of 5 days to 325 mg propafenone hydrochloride (as prolonged-release capsules) given every twelve hours. If additional therapeutic effect is needed, the dose of propafenone hydrochloride (as prolonged-release capsules) may be increased to 425 mg given every twelve hours after a minimum of another 5 day interval. To facilitate dose titration, additional strengths of propafenone SR are available. Direct comparison of propafenone SR capsules with propafenone IR (immediate/instant release) tablets has not been studied in clinical trials.

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.

Dosage in impaired liver function: propafenone is extensively metabolised via a saturable hepatic oxidase pathway. In view of the increased bioavailability and elimination half-life of propafenone, a reduction in the recommended dose may be necessary.

Dosage in impaired renal function: the elimination of propafenone’s major metabolite is affected by renal impairment therefore Arythmol SR should be administered cautiously.

Elderly: No overall differences in safety or effectiveness were observed in this patient population, however greater sensitivity of some older individuals can not be ruled out, therefore these patients should be carefully monitored.

Dose titration should be performed with special caution in these patients.

Arythmol SR should be taken with water, either with or without food.

Do not crush or further divide the contents of the capsule.

Arythmol SR has not been studied in children and adolescents.

4.3 Contraindications

- Hypersensitivity to propafenone hydrochloride
- Hypersensitivity to soya or any of the other excipients
- Hypersensitivity to peanut
- Known Brugada syndrome
- Significant structural heart disease such as:
  - Incident of myocardial infarction within the last 3 months.
  - 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 AV block, 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

It is essential that each patient given Arythmol SR be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to Arythmol SR 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 may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

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

As with **some** other Class 1C anti-arrhythmic agents, patients with significant structural heart disease may be predisposed to serious adverse events. Therefore Arythmol SR is contraindicated in these patients (see section 4.3).

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

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.

No significant effects on the pharmacokinetics of propafenone or lidocaine have been observed following their concomitant use in patients: However, concomitant use of propafenone and lidocaine has been reported to increase the risks of central nervous system adverse reactions of lidocaine.

Combination therapy of amiodarone and propafenone hydrochloride can affect conduction and repolarization and lead to abnormalities that have the potential to be proarrythmic.

Dose adjustments of both compounds based on therapeutic response may be required.

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.

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).

Coadministration of propafenone hydrochloride with drugs metabolized by CYP2D6 (such as venlafaxine) might lead to increased levels of these drugs. Increased plasma levels and/or blood levels of propranolol, metoprolol, desipramine, cyclosporin, 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.

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 therapy should be monitored during concomitant chronic phenobarbital and/or rifampicin treatment.

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.

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 Arythmol SR 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 Arythmol SR prolonged release hard capsules.

The reactions considered at least possibly related to Arythmol SR 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.

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 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	
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

c. Description of selected adverse reactions

Conduction disorders
The most frequent presentation is atrioventricular block first degree which is usually asymptomatic but may require monitoring and reduction of dose to prevent higher grade conduction blocks.

Dose related adverse reactions
Dysgeusia and nausea may be dose related.

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 and ventricular fibrillation. Reduction of contractility (negative inotropic effect) can 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 extremely rare cases, 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

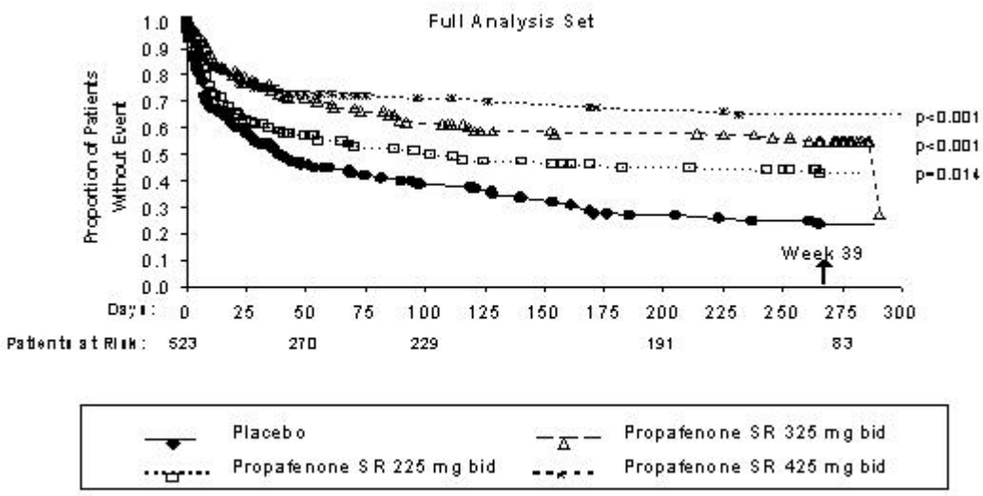
ATC code C01BC03.

Propafenone is an antiarrhythmic agent with membrane-stabilising, sodium channel blocking properties (Vaughan Williams, class 1C). It also possesses weak beta blocking efficacy (class II according to Vaughan Williams). Propafenone 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 prolongs the refractory periods in the accessory pathways in patients with Wolff-Parkinson-White syndrome (WPW syndrome).

In 2 double-blind Phase III trials Arythmol SR has been evaluated in patients with recurrent episodes of symptomatic atrial fibrillation.

In one US multicentre study (RAFT), 3 doses of Arythmol SR (225 mg bid, 325 mg bid and 425 mg bid) and placebo were compared in 523 patients. The patients had a median history of atrial fibrillation of 13 months and documented symptomatic atrial fibrillation within 12 months of study entry. Over 90% were NYHA Class I and 21% had a prior electrical cardioversion. All three doses of Arythmol SR administered for up to 39 weeks were shown to be superior to placebo for the time to the first recurrence of symptomatic atrial arrhythmia from day 1 of randomisation. ($p<0.014$ for 225 mg bid and <0.001 for 325 mg and 425 mg bid).

Figure 1: Tachycardia-free period (absence of symptomatic AF, atrial flutter or PSVT) from Day 1 of randomisation (full analysis set); RAFT (log-rank test)



A dose-response to Arythmol SR was prominent for the following analyses: time to recurrence of symptomatic atrial arrhythmia from Day 1 of randomisation and time to recurrence of symptomatic atrial arrhythmia from Day 5 of randomisation. There was a clear dose response observed in the tachycardia-free period with 425 mg bid group demonstrating the longest time to recurrence. Nevertheless, regarding the safety parameters, it appears that propafenone SR 425 mg bid has a less favourable safety profile than propafenone 325 mg and 225 mg bid.

In a European multicentre trial (ERAFT), 2 doses of Arythmol SR (325 mg bid and 425 mg bid) and placebo were compared in 293 patients. Patients had a median duration of atrial fibrillation of 3.3 years, 37% had a history of minor structural heart disease and 61% were taking medications that lowered heart rate. During a qualifying period of up to 28 days, patients had to have 1 documented incident of symptomatic atrial fibrillation. The double-blind treatment phase consisted of a 4-day loading period followed by a 91-day efficacy period. Symptomatic arrhythmias were documented by electrocardiogram monitoring Arythmol SR was shown to prolong the time to the first recurrence of symptomatic atrial arrhythmia from Day 5 of randomisation (primary efficacy analysis) in a dose dependent manner: 9 days in the placebo group, 35 days in the propafenone SR 325 mg bid group (p=0.004) and 44 days in the propafenone SR 425 mg bid group (p=0.003).

The results are consistent with RAFT.

5.2 Pharmacokinetic properties

Metabolism:

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.

As a result of the increased first pass effect, higher daily doses of propafenone are required from the SR formulation relative to the immediate release formulation, to obtain similar exposure to propafenone hydrochloride.

There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolised with an elimination half-life from 2 - 10 hours. These patients metabolise propafenone into two active 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.

Maximal plasma levels of propafenone are reached between 3 - 8 hours following the administration of Arythmol SR. The estimated propafenone elimination half-life ranges from 10 - 32 hours.

In extensive metabolisers, the saturable hydroxylation pathway (CYP2D6) results in nonlinear pharmacokinetics. The effective dose of propafenone appears to be the same regardless of the metabolic status (poor vs. rapid metaboliser) of the patient. In addition, since steady-state conditions are reached by 5 days in both groups of patients no change in the dosing titration strategy is required.

Data from relative bioavailability assessments contained in a pharmacokinetic study comparing different dosages and formulations of prolonged release (SR) and immediate release (IR) propafenone demonstrated that comparable exposures (AUCs) of propafenone occurred with 150 mg propafenone IR tablets administered three times a day and 325 mg Arythmol SR capsules administered twice a day, as well as 300 mg propafenone IR tablets administered twice a day and 425 mg Arythmol SR capsules administered twice a day. A switch to Arythmol SR capsules in patients being treated with propafenone IR tablets, however, has not been explicitly studied in a clinical trial.

The dosage must be adjusted in patients with liver disease. Arythmol SR should be administered cautiously in patients with renal disorder. Please see section 4.2.

Although food increased bioavailability in a single dose study, during multiple dose administration of propafenone SR to healthy volunteers, food did not have a major impact on the absorption of propafenone SR.

Inter/Intra Subject Variability:

With propafenone, there is a considerable degree of interindividual variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear pharmacokinetics in extensive metabolisers. The large intersubject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity.

5.3 Preclinical safety data

Preclinical 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

Capsule contents
Hypromellose
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide E 171
Sodium laurilsulfate

Printing ink
Ferric Oxides and Hydroxides, E 172 (Red Ferric Oxide)
Shellac
Propylene Glycol
Potassium Hydroxide
Ammonia Solution, concentrated
Butyl Alcohol
Ethanol, anhydrous
Isopropyl Alcohol
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVDC/aluminium or Polypropylene/aluminium blister containing 20, 50, 60 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ireland Ltd
4051 Kingswood Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 38/79/6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 March 2006
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10 DATE OF REVISION OF THE TEXT

September 2012