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.
White to off-white film-coated tablet, biconvex and embossed “150” on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic supraventricular tachyarrhythmias requiring treatment, such as AV junctional tachycardia, supraventricular tachycardia in patients with Wolff-Parkinson-White (WPW) syndrome or paroxysmal atrial fibrillation.

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

4.2 Posology and method of administration

The dosage is to be adjusted to the individual patient’s requirements.

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.

Adults:
A daily dose of 450 to 600 mg of propafenone hydrochloride, divided in two or three doses per day, is recommended in the titration 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 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, 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.

Liver/Renal Impairment:
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.

Children:
Arythmol tablets are not recommended for use in children.

Method of administration:
Owing to the bitter taste and surface anesthetic action of propfaenone, the film-coated tablets should be swallowed whole (without chewing) with liquid.

4.3 Contraindications

- Hypersensitivity to the active ingredient propafenone hydrochloride and excipients listed in Section 6.1
- Known Brugada syndrome (See Section 4.4)
- 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
    - 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
- Myasthenia gravis

Concomitant treatment with ritonavir

4.4 Special warnings and precautions for use

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. Pacemakers function should therefore be checked and, if necessary, re- programmed.

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

As with other class Ic antiarrhythmic agents, patients with significant structural heart disease may be predisposed to serious adverse events, therefore, propafenone hydrochloride is contraindicated in these patients (see section 4.3).

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

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products 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.

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 lidocaine has been reported to increase the risks of central nervous adverse reactions of lidocaine.

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.

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 metabolisers increased the S-propafenone C_{max} and AUC by 39 and 50% and the R-propafenone C_{max} and AUC by 71 and 50%. Lower doses of propafenone may be sufficient to achieve the desired therapeutic response.

A possible potentiation of drug side effects may occur when propafenone hydrochloride 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).

Co-administration of propafenone hydrochloride with drugs metabolised 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. Doses of these medicinal products should be reduced, as appropriate, if signs of overdose are observed.

Due to the potential for increased plasma concentrations, co-administration of ritonavir and propafenone hydrochloride is contraindicated (see section 4.3).
Phenobarbital is 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 anti-coagulants (e.g. phenoprocoumon, warfarin) is recommended as propafenone hydrochloride may enhance the efficacy of these medicinal products resulting in an increased prothrombin time. Doses of these medicinal products should be adjusted if necessary.

Caution should be taken with regards to digitalis toxicity.

Special Populations:

Paediatric population
Interaction studies have only been performed in adults. It is not knows whether the extent of interactions is similar in the paediatric aged group to that in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Propafenone hydrochloride 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 concentration of propafenone in the umbilical cord has been reported to be about 30% of that of 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 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 (≥1/1000 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 ≥1/1000 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

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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie.

4.9 Overdose

Symptoms of overdosage:

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 automaticity, AV block, ventricular tachycardia, ventricular flutter 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 severe cases of overdosage, tonic-clonic convulsions, paraesthesia, somnolence, coma and respiratory arrest may occur.

In extremely rare cases, convulsions have been reported on overdose. Somnolence and death has also been reported.

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 isoprenaline 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

Mechanics of action and pharmacodynamic effects
Propafenone hydrochloride is an antiarrhythmic agent with a membrane stabilising, sodium channel blocking properties (Vaughan Williams, class Ic). 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 in patients with WPW syndrome.

5.2 Pharmacokinetic properties

Absorbtion*:*
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-dependant absolute bioavailability.
Although food increased the maximum plasma concentration and bioavailability in a single dose study, during multiple dose administration of prepafenone 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 ng/mL to 91.3% at 100 ng/mL.

Biotransformation and elimination:
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 (i.e., extensive metabolisers). 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 (i.e., poor metabolisers).

The estimated propafenone elimination half-life ranges from two to ten hours for extensive metabolisers and from ten to 32 hours for poor metabolisers. Clearance of propafenone is 0.67 to .081 L/h/kg.

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

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

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 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.

Elderly population
Proafenone 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.

Paediatric population
Arythmol is not recommended for the use in children.

Renal impairment
In patients with renal impairment, exposure to prepafenone and 5-hydroxypropafenone was similar to tha in healthy controls, while accumulation of glucuronide metabolites was observed. Propafenone hydrochloride should be administered cautiously in patients with renal disease.

*Hepatic impairmen*t
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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose,
Maize starch,
Croscarmellose sodium,
Hypromellose,
Magnesium stearate.

Tablet coating:
Hypromellose,
Macrogol 400,
Macrogol 6000,
Titanium dioxide (E 171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium blister strips packed in cartons.
Pack size: 90.

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 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/048/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 July 1983

Date of last renewal: 20 July 2008

10 DATE OF REVISION OF THE TEXT

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