Propafenone

Core Safety Profile

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 propafenone be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to propafenonesupports 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 other Class 1C anti-arrhythmic agents, patients with significant structural heart disease may be predisposed to serious adverse events. Therefore propafenoneis 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 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.

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 Arrythmia[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

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.