4. CLINICAL PARTICULARS

4.2 Posology and method of administration

Propafenone SR

The dose of propafenone 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.

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 SR 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 propafenone 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.

Propafenone SR has not been studied in children and adolescents.

Propafenone IR

Oral

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 has been receiving treatment for three to four days.

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.

The individual maintenance dose should be determined under cardiological surveillance including ECG monitoring and repeated blood pressure control (titration phase).
**Children**
In children, an average daily dose of 10 to 20 mg of propafenone hydrochloride per kilogram body weight given in three to four doses has proven to be appropriate in the dose titration phase and maintenance treatment.

Dose increases should not be attempted until the patient has been receiving treatment for three to four days.

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

**Elderly**
In elderly patients or patients with relevant impairment of left ventricular function (left ventricular ejection fraction less than 35%) or structural myocardial disease, 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.

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.

**Intravenous**
The dosage should be tailored to the individual and determined under ECG and blood pressure monitoring. When administering infusions, close monitoring of the ECG (QRS interval, PR interval and QTc interval) and circulatory parameters is required.

The single dose is 1 mg/kilogram body weight. The desired therapeutic effect is often achieved at a dose of 0.5 mg/kilogram body weight. If necessary, the single dose may be raised to 2 mg/kg body weight. Treatment should be initiated at the lowest possible dose level while keeping the patient under careful observation and close ECG and blood pressure monitoring.

Intravenous injections should be administered slowly, within a period of three to five minutes and the interval between injections should not be less than 90 to 120 minutes. If there is QRS widening or a rate-dependent prolongation of the QT interval of more than 20%, the injection should be immediately discontinued.

**Short-term infusion**
When administering propafenone hydrochloride by short-term infusion lasting one to three hours, the dosing rate is 0.5 to 1 mg/minute.

**Slow intravenous infusion**
When administering propafenone hydrochloride by slow intravenous infusion, the highest daily dose is generally 560 mg. Glucose or fructose solution (5%) should be used for making up the infusion. Isotonic saline is not suitable for making up the infusion solution due to the potential for precipitation.

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 propafenone 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 other Class 1C anti-arrhythmic agents, patients with significant structural heart disease may be predisposed to serious adverse events. Therefore propafenone 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 proaryrrhythmic. 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 antiarrhythmic 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.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common ≥1/10</th>
<th>Common ≥ 1/100 to &lt; 1/10</th>
<th>Uncommon ≥1/1,000 to &lt; 1/100</th>
<th>Not Known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
<td>Agranulocytosis, Leukopenia, Granulocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity¹</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Anxiety</td>
<td>Sleep disorders</td>
<td>Nightmare</td>
<td>Confusional state</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness²</td>
<td>Headache</td>
<td>Syncope</td>
<td>Convulsion, Extrapyramidal symptoms, Restlessness</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac conduction disorders³</td>
<td>Sinus bradycardia, Bradycardia, Tachycardia, Atrial flutter</td>
<td>Ventricular tachycardia, Arrhythmia⁴</td>
<td>Ventricular fibrillation, Cardiac failure⁵, Heart rate reduced</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td>Hypotension</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td>Dyspnoea</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, Vomiting, Nausea, Diarrhoea, Constipation, Dry mouth</td>
<td>Abdominal distension, Flatulence</td>
<td>Retching, Gastrointestinal disturbance</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatic function abnormal⁶</td>
<td></td>
<td></td>
<td>Hepatocellular injury, Cholestasis, Hepatitis, Jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td>Lupus-like syndrome</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Chest pain, Asthenia, Fatigue, Pyrexia</td>
<td></td>
<td></td>
<td>Sperm count decreased¹</td>
</tr>
</tbody>
</table>

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.