Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rythmodan 150mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150mg of Disopyramide.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule
Hard opaque capsule containing a white powder and consisting of an opaque white body and cap. The capsule is printed in black, RY underlined on one part and 150 on the other part

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of patients with various atrial and ventricular arrhythmias, singly or in combination.

4.2 Posology and method of administration

Adults Only:

The initial dose ranges from 400-600 mg daily in divided doses every six hours. The dose may subsequently be adjusted up to 800 mg if so required. In the presence of impaired renal function the following schedule is suggested with a reduction in dosage dependent directly on Creatinine Clearance.

Creatinine Clearance ml/min	Dosage mg	Dosage interval
20-60	100 or 150	8 hour 12 hour
8-20	100	12 hour
<8	150	24 hour

The drug's use and effects in children have not been studied adequately for recommendations to be made for paediatric dosage.

Elderly:

A dose reduction due to reduced renal and hepatic function in the elderly (especially elderly non-smokers) should be considered (see section 4.4).

4.3 Contraindications

Use in patients with pre-existing heart block (if no pacemaker is present) shock, or untreated urinary tract obstruction.

Use in patients with cardiomyopathy or congestive heart failure unless adequately controlled and digitalized.

The drug should not be used in patients with hypersensitivity to disopyramide.

4.4 Special warnings and precautions for use

In view of the serious nature of many of the conditions being treated, it is suggested that Rythmodan injection should only be used when facilities exist for cardiac monitoring or defibrillation, should the need arise.

Antiarrhythmic drugs belonging to the class IC (Vaughan Williams classification) were included in the cardiac arrhythmia suppression trial (CAST), a long term multicentre randomised, double blind study in patients with asymptomatic non life-threatening ventricular arrhythmia who have had a myocardial infarction more than six days but less than two years previously. A significant increase in mortality and non-fatal cardiac arrest rate was seen in patients treated with class IC antiarrhythmic drugs when compared with a matched placebo group. The applicability of the CAST results to other antiarrhythmics and other populations (eg. those without recent infarction) is uncertain. At present, it is best to assume that the risk extends to other antiarrhythmic agents for patients with structural heart disease.

There is no evidence that prolonged suppression of ventricular premature contractions with antiarrhythmic drugs prevents sudden death.

All antiarrhythmic drugs can produce unwanted effects when they are used to treat symptomatic but not life threatening arrhythmia; the expected benefits should be balanced against their effects.

In patients with structural heart disease, proarrhythmia and cardiac decompensation are special risks associated with antiarrhythmic drugs. Special caution should be exercised when prescribing in this context.

Haemodynamically significant arrhythmias are difficult to treat and affected patients have a high mortality risk. Treatment of these arrhythmias, by whatever modality, must be initiated in hospital.

Owing to its negative inotropic effect, disopyramide should be used with caution in patients suffering from significant cardiac failure. This group may be specially sensitive to the negative inotropic properties of disopyramide. Such patients should be fully digitalised or controlled with other therapy before treatment with disopyramide is commenced.

Aggravation of existing arrhythmia, or emergence of a new type of arrhythmia, demands urgent review of disopyramide treatment.

Similarly, if an atrioventricular block or a bifascicular block occurs during treatment, the use of disopyramide treatment should be reviewed.

There have been reports of ventricular tachycardia, ventricular fibrillation, and torsade de pointes in patients receiving disopyramide. These have usually, but not always, been associated with significant widening of the QRS complex or prolonged QT interval. The QT interval and QRS duration must be monitored and disopyramide should be stopped if these are increased by more than 25%. If these changes or arrhythmias develop the drug should be discontinued. Disopyramide should be used with caution in patients with atrial flutter or a trial tachycardia with block as conversion of a partial AV block to a 1:1 response may occur leading to a potentially more serious tachyarrhythmia.

The occurrence of hypotension following disopyramide administration requires prompt discontinuation of the drug. This has been observed especially in patients with cardiomyopathy or uncompensated congestive heart failure. Any resumption of therapy should be at a lower dose with close patient monitoring. Disopyramide should be used with caution in the treatment of digitalis intoxication.

Potassium imbalance: antiarrhythmic drugs may be hazardous in patients with potassium imbalance, as potassium abnormalities can induce arrhythmias.

During treatment with disopyramide, potassium levels should be checked regularly. Patients treated with diuretics or

stimulant laxatives are at particular risk of hypokalaemia.

Renal insufficiency: in renal insufficiency, the dosage of disopyramide should be reduced by adjusting the interval between administrations.

Hepatic insufficiency: hepatic impairment cause an increase in the plasma half-life of rythmodan and a reduced dosage may be required.

Hypoglycaemia: hypoglycaemia has been reported in association with disopyramide administration. Patients at particular risk are the elderly, the malnourished, or diabetics. The risk of hypoglycaemia occurring is increased with impaired renal function or cardiac failure. Blood glucose should be monitored in all patients. Strict adherence to the dosing recommendations is advised. If hypoglycaemia occurs then treatment with disopyramide should be stopped.

Atropine-like effects: there is risk of:

- Ocular hypertension in patients with narrow-angle glaucoma.
- Acute urinary retention in patients with prostatic enlargement.
- Aggravation of myasthenia gravis.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with other antiarrhythmic drugs: combinations of antiarrhythmics drugs are not well researched and their effect may be unpredictable. Thus, antiarrhythmic combination should be avoided except under certain circumstances, eg. beta-blockers for angina pectoris; digoxin with beta-blocker and/or verapamil for the control of atrial fibrillation, when defined as effective for an individual.

Interaction with drugs associated with risk of torsade de pointe, such as:

- Tricyclic and Tetracyclic Antidepressants.
- Intravenous Erythromycin.
- Astemizole; cisapride; pentamidine; pimozide; sparfloxacin; terfenadine.

The concomitant use of these medications whilst undergoing treatment with disopyramide increases the chance of cardiac arrhythmia.

There is some evidence that disopyramide is metabolised by hepatic CYP3A. Concomitant administration of significant inhibitors of this isozyme (e.g. certain macrolide of azole antifungal antibiotics) may therefore increase the serum levels of disopyramide. On the other hand, inducers of CYP3A (e.g. rifampicin, certain anticonvulsants) may reduce disopyramide and increase mn-diisopyramide serum levels. Since the magnitude of such potential effects is not foreseeable, such drug combinations are not recommended.

When prescribing a drug metabolised by CYP3A [such as theophylline, HIV protease inhibitor (e.g. ritonavir, indinavir, saquinavir, cyclosporin A, warfarin] it should be kept in mind that disopyramide is probably also a substrate of this isozyme and thus competitive inhibition of metabolism might occur, possibly increasing serum levels of these drugs.

Interactions with hypokalaemia inducing drugs: concomitant use with drugs that can induce hypokalaemia such as: diuretics, amphotericin B, tetracosactrin (corticotrophin analogue), gluco and mineralocorticoids may reduce the action of the drug, or potentiate proarrhythmic effects. Stimulant laxatives are not recommended to be given concomitantly, due to their potassium lowering potential.

Other Drug Interactions:

Atropine and other anticholinergic drugs, including phenothiazines, may potentiate the atropine-like effects of disopyramide.

4.6 Pregnancy and lactation

Pregnancy:
Although Rythmodan has undergone animal tests for teratogenicity without evidence of any effect on the developing foetus, its safety in human pregnancy has not been established. Disopyramide has been reported to stimulate contractions of the pregnant uterus. The drug should only be used during pregnancy if benefits clearly outweigh the possible risks to the mother and foetus.

Lactation:
No data for Rythmodan injection, but studies have shown that oral Rythmodan is secreted in breast milk although no adverse effects to the infant have been noted. However, clinical experience is limited and Rythmodan should only be used in lactation, if, in the clinicians judgement, it is essential for the welfare of the patient. The infant should be closely supervised, particularly for anti-cholinergic effects and drug levels determined if necessary. Ideally, if the drug is considered essential an alternative method of feeding should be used.

4.7 Effects on ability to drive and use machines

Some adverse reactions may impair the patients' ability to concentrate and react, and hence the ability to drive or operate machinery. (See section 4.8).

4.8 Undesirable effects

Cardiac: it is accepted that the arrhythmogenic potential of disopyramide is weak. However, as with all antiarrhythmics drugs, disopyramide may worsen or provoke arrhythmias. This proarrhythmic effect is more likely to occur in the presence of hypokalaemia with the associated use of antiarrhythmic drugs, in patients with severe structural heart disease or with prolongation of the QT interval.

Intra-cardiac conduction abnormalities may occur: QT interval prolongation, widening of the QRS complex, atrioventricular block and bundle-branch block.

Other types of arrhythmia have been reported: bradycardia, sinus block.

Episodes of severe heart failure or even cardiogenic shock have also been described particularly in patients with severe structural heart disease. The resulting low cardiac output can cause hypotension, renal insufficiency and/or acute hepatic ischaemia.

Other adverse reactions include:

Atropine like: urinary (dysuria, acute urinary retention); ocular (disorders of accommodation, diplopia); gastrointestinal - (dry mouth, abdominal pain; nausea, vomiting, anorexia, diarrhoea, constipation), impotence; psychiatric disorders.

Skin reactions: very rarely, rashes; isolated reports of anaphylactic-type reactions possibly culminating in shock (only reported in association with the injectable formulation).

Rarely: hypoglycaemia.
Very Rarely: cholestatic jaundice, headache, dizzy sensation, neutropenia.

Rapid infusion may cause profuse sweating.

4.9 Overdose

There is no specific antidote for disopyramide. Prostigmine derivatives can be used to treat anticholinergic effects. Symptomatic supportive measures may include: early gastric lavage; administration of a cathartic followed by activated charcoal by mouth or stomach tube; IV administration of isoprenaline, other vasopressors and/or positive inotropic agents; if needed - infusion of lactate and/or magnesium, electro-systolic assistance, cardioversion, insertion of an intra-aortic balloon for counterpulsion and mechanically assisted ventilation. Haemodialysis, haemofiltration or haemoperfusion with activated charcoal has been employed to lower serum concentrations of the drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Rythmodan is a “Class 1A” antiarrhythmic.

5.2 Pharmacokinetic properties

Rythmodan is well absorbed, metabolised by dealkylation and excreted through the kidney, with a six hour half-life, increased in patients with congestive heart failure.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Magnesium stearate
Pregelatinised starch
Talc
Gelatin
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Amber glass bottle with jay cap closure containing 100 capsules. PVC/PVdC blister strips in cardboard cartons containing 84 capsules.

Not all pack sizes may be marketed.

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.

7 MARKETING AUTHORISATION HOLDER

Hoechst Marion Roussel Ireland Limited
Cookstown
Tallaght
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 855/37/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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August 2004