Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rythmodan 50 mg/5 ml Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Disopyramide phosphate equivalent to 50 mg disopyramide in 5 ml of solution (i.e. 10 mg/ml).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion
Rythmodan injection is a clear colourless solution for injection or infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rythmodan Injection is intended for intravenous use only and is indicated for the treatment of patients with various atrial and ventricular arrhythmias, singly or in combination.

4.2 Posology and method of adminstration

Adults including the Elderly:
The recommended dosage can be given by two different regimes:

1. An initial bolus injection of 2mg/kg (but not exceeding 150mg irrespective of body weight) should be given SLOWLY OVER NOT LESS THAN FIVE MINUTES. If conversion occurs during this time the injection should be stopped. If the arrhythmia is to respond to Rythmodan it will usually do so within 10–15 minutes after completion of the injection.
   Transfer to oral maintenance therapy is accomplished by giving 200mg orally immediately on cessation of intravenous administration followed by 200mg every eight hours for 24 hours. Subsequently maintenance is often achieved by a total daily dosage of 400-600mg daily.
   If conversion is achieved by intravenous Rythmodan but the arrhythmia subsequently recurs, a further slow bolus injection may be administered cautiously and preferably under ECG control.
   The total administration by the intravenous route should not exceed 4mg/kg (maximum 300mg) in the first hour, nor should the combined administration by the intravenous and oral routes exceed 800mg in 24 hours.

2. An initial bolus injection as above, i.e. over not less than five minutes, maintained by infusion of 20–30mg/hour (or 0.4mg/kg/hour) up to a maximum of 800mg daily.
   This regime should be employed if the patient is unable to take oral medication in particularly serious arrhythmias being treated in coronary care units.

If the patient has impaired renal function, a reduced oral dosage or its infused equivalent may be desirable.
Hepatic impairment: Causes an increase in the plasma half-life of Rythmodan, a reduced dosage may be required as for renal impairment.

4.3 Contraindications

Contra-indications: 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 digitalised.
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 1C (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 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 1C antiarrhythmic drugs when compared with a matched placebo group. The applicability of the CAST results to other antiarrhythmics and other populations (e.g. 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 benefit should be balanced against their risks.
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 taken 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 especially 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 disopyramide treatment.
Similarly, if an atrioventricular block or a bifasicular block occurs during treatment, the use of disopyramide 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 atrial 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 causes 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 a 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 antiarrhythmic 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 Pointes, such as
– tricyclic and tetracyclic antidepressants
– intravenous erythromycin
– astemizole ; cisapride ; pentamidine ; pimoxide ; 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 or azole antifungal antibiotics) may therefore increase he serum levels of disopyramide. On the other hand, inducers of CYP3A (e.g. rifampicin, certain anticonvulsants) may reduce disopyramide and increase MN–disopyramide 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 inhibitors (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 mineralo–corticoids 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 disopyramide is secreted in breast milk, although no adverse effects to the infant have been noted. However, clinical experience is limited and disopyramide should only be used in lactation if, in the clinician's judgement, it is essential for the welfare of the patient. The infant should be closely supervised, particularly for anticholinergic 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 antiarrhythmic 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 ischemia.
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 the serum concentration of the drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Disopyramide is a Class 1 antiarrhythmic agent with a depressant action on the heart similar to that of quinidine and is used for the prevention and treatment of a wide variety of cardiac arrhythmias.

5.2 Pharmacokinetic properties

Following intravenous administration, disopyramide is rapidly distributed. Doses of 1.5–2mg/kg produce plasma levels of about 10microg/ml, declining rapidly to 3.8–4.2microg/ml at 5 minutes and to less than 3microg/ml at 15 minutes. In multidose studies, direct slow intravenous injection of 2mg/kg followed by an infusion of 20mg/hr, maintained plasma levels of disopyramide between 2.5 and 2.8microg/ml from the first hour onwards.
Distribution T1/2: 2–4 minutes in healthy volunteers. Longer (15 minutes) in patients with acute myocardial infarct.
Elimination Phase of Plasma T1/2: 5–8 hours. Increased in renal impairment, cardiac and hepatic disease.
Protein Binding: 50–60%. Saturable and concentration dependent.
Volume of Distribution: Variable according to method of determination
Metabolism: Approximately 25% of a dose metabolised to a mono–n–dealkylated derivative. Additional 10% as other metabolites.
Excretion: 75% unchanged drug via urine, remainder in faeces. Mono–n–dealkylated metabolite 25% in urine, 64% via faeces.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl Alcohol
Sorbitol
Water for injection

6.2 Incompatibilities

None listed.

6.3 Shelf Life

3 years.
Once opened use immediately.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Type I Ph. Eur. clear colourless glass 5 ml ampoules.

Pack size: 5 ampoules.

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

Rythmodan Injection has been found to be physically compatible with the following:

Sodium Chloride Injection BP
Dextrose Injection BP
Compound Sodium Lactate Injection BP

7 MARKETING AUTHORISATION HOLDER

Roussel Laboratories Ltd.
Broadwater Park
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Middlesex UB9 5HP
UK

8 MARKETING AUTHORISATION NUMBER

PA 6/5/1

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