Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rythmodan Retard 250 mg Prolonged-release Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250mg disopyramide (as phosphate)
Excipients: Contains 30mg Sucrose and 3.5mg anhydrous glucose

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.
Whitish, circular, biconvex film-coated tablets having a single scoreline on one face. On one surface is “O13” and “E” and on the other side the Russel Uclaf logo.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Route of administration: The usual daily dose is one tablet in the morning and evening.

Tablets should be swallowed whole, not crushed, bitten or chewed.

Children: Not recommended (see section 4.3).

4.3 Contraindications

Disopyramide is contra–indicated
- In second or third degree heart block and sinus node disease if no pacemaker is present.
- Bundle branch block associated with first degree atrioventricular block.
- Double block (left posterior or anterior hemiblock and RBBB)
- Pre-existing long QT
- Severe sinus node dysfunction
- Severe heart failure, unless secondary to cardiac arrhythmia (see section 4.4)
- Concomitant administration with other antiarrhythmics or other drugs liable to provoke ventricular arrhythmias and especially torsades de pointes (see Section 4.5)
- Cardiogenic shock
- Hypersensitivity to disopyramide

The sustained release formulation is contraindicated in children and in patients with renal or hepatic impairment.

4.4 Special warnings and precautions for use

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 1C 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.

Life threatening and haemodynamically significant arrhythmia are difficult to treat and affected patients are at high risk. Treatment of these arrhythmias, whatever modality, must be initiated in the hospital.

Disopyramide phosphate should be avoided in patients with glaucoma. In patients with a history or family history of glaucoma, intraocular pressure should be measured before initiating treatment (see also section 4.8).

There is no evidence that prolonged suppression of ventricular premature contractions with antiarrhythmic drugs prevents sudden death. Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmia. For these reasons, antiarrhythmic drugs should not be prescribed for the treatment of patients with asymptomatic ventricular premature contractions, haemodynamically non significant.

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 risks.

Patients with structural heart disease may be specially sensitive to the depressive effect (negative inotropic properties) of disopyramide. Treatment should be given under strict supervision and the cardiac function monitored.

Disopyramide should not be used in patients with uncompensated congestive heart failure, unless this heart failure is secondary to cardiac arrhythmia. If disopyramide is to be given under these circumstances, special care and monitoring are essential.

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 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.

<u>Potassium imbalance:</u> Potassium abnormalities can by themselves induce arrhythmia and serum potassium must therefore be monitored. Any potassium imbalance should be corrected, particularly when diuretics are given concomitantly.

Antiarrhythmic drugs may be hazardous in patients with hypokalaemia.

During treatment with disopyramide, potassium levels should be checked regularly and corrected if necessary. Patients treated with diuretics or stimulant laxatives are at particular risk of hypokalaemia.

<u>Renal or hepatic impairment:</u> The sustained release formulation is contraindicated in patients with renal or hepatic

impairment.
There is no experience with the sustained release tablets in patients with renal insufficiency, hepatic insufficiency, and children.

Hypoglycaemia: Hypoglycaemia has been reported in association with disopyramide administration. Given the risk of hypoglycaemia, sometimes severe, particularly in elderly or malnourished subjects, treated diabetics and patients with renal insufficiency, blood sugar levels should be monitored in these patients. 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,
– paralytic ileus, especially in elderly, in a context of concomitant use with anticholinergic drugs or increase plasma level of disopyramide (see above section 4.4 relating to renal or hepatic impairment, section 4.5 and 4.9)
- aggravation of myasthenia gravis.
- cognitive disorders that require medical attention in elderly patients. For other atropine-like effects, see section 4.8 Undesirable effects.

Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase –isomaltase insufficiency should not take this medicine.

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 by specialised procedure. Antiarrhythmics
(Vaughan Williams classification):
- Class I; most drugs, including phenytoin
- Class II; beta-blocking drugs
- Class III; amiodarone, bretylium, d-sotalol, ibutilide
- Class IV; verapamil, diltiazem, lidoflazine, bepridil.

Interaction with drugs associated with risk of Torsade de Pointes, such as
– tricyclic and tetracyclic antidepressants
– intravenous erythromycin, vincamine, sultopride
– 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 the 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), ciclosporin 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, tetracosactide (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 (see section 4.4 and 4.8).

As in vitro study has shown that roxithromycin can displace protein-bound disopyramide; such a competitive protein-binding effect could result in increased serum levels of free disopyramide in vivo.

Phosphodiesterase Type 5 Inhibitors
There is evidence that phosphodiesterase Type 5 Inhibitors may be potentially associated with a risk of QT prolongation. Concomitant administration of disopyramide with such drugs may potentially enhance this QT prolongation effect and is not recommended.

4.6 Fertility, 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. Rythmodan has been reported to stimulate contractions of the pregnant uterus, it passes into fetal circulation. Rythmodan should not be used during pregnancy unless the clinical condition of the woman requires treatment with disopyramide.

Lactation : Disopyramide metabolites are excreted in human milk and the effect on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Rythmodan therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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 Below).

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 ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation and torsades de pointes). This proarrhythmic effect is more likely to occur in the presence of hypokalaemia and/or the associated use of antiarrhythmic drugs and/or in patients with severe structural heart disease and/or 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 mimicking acute hepatocellular hepatitis.

Other adverse reactions include:
Atropine like effects see also section 4.4 : Urinary (dysuria ; acute urinary retention, especially in prostatism) ; ocular (disorders of accommodation ; diplopia) ; gastrointestinal -(dry mouth ; constipation); cognitive disorders Epigastralgia, nausea, vomiting, anorexia, diarrhoea; impotence ; psychiatric disorders.

Skin reactions:– very rarely, rashes ; isolated reports of anaphylactic–type reactions (e.g. urticaria, angioedema) possibly culminating in shock (essentially reported in association with the injectable formulation). Agranulocytosis.

Rarely: Hypoglycaemia, sometimes severe (see section 4.4 - hypoglycaemia)
Very rarely: cholestatic jaundice, headache, dizzy sensation, neutropenia.

4.9 Overdose

Toxic plasma levels are reflected by ECG abnormalities such as:

- marked prolongation of QT interval as a premonitory sign of other arrhythmias, in particular torsades de pointes which can result in repeated syncopes
- widening of the QRS complex
- variable degrees of atrioventricular block

The clinical signs of overdose may include:

- paralytic ileus, bilateral mydriasis
- syncope, hypotension and shock
- cardiac arrest due to intraventricular block or asystole
- respiratory symptoms
- coma (with bilateral mydriasis) in cases of massive intoxication

Apart from prostigmine derivatives which can be used to treat anticholinergic effects, there is no specific antidote for disopyramide.

Treatment of acute overdose should be carried out in an intensive care unit under continuous cardiac monitoring. Symptomatic therapeutic measures may include:

- early gastric lavage
- administration of a cathartic followed by activated charcoal by mouth or stomach tube
- IV administration of isoproterenol and/or other vasopressors and/or positive inotropic agents
- if needed; infusion or lactate and/or magnesium, electro-systolic assistance, cardioversion, insertion of an intra-aortic balloon for counterpulsation, 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 I 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

The dissolution characteristics of Rythmodan Retard are designed to release 250mg disopyramide over 12 hours. The dissolution profile is matched to the drug half life of 6-8 hours with good therapeutic levels followed by steady release of disopyramide to sustain therapeutic effect.

The sustained release mechanism is based on the matrix principle, adapted for disopyramide. Reliable release is achieved by strict control of particle size.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol monostearate 40-55 Type II
Sucrose

Povidone K30
Magnesium stearate

Film-coating
Hypromellose
Propylene glycol
Anhydrous Glucose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

White opaque PVC/PVDC blister containing 60 tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Ltd. T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/069/004

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