

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rythmodan 100mg Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsule containing Disopyramide 100mg.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules have a green cap and yellow body and are printed in black ink with RY on one part and RL on the other

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rythmodan is used in the treatment of cardiac arrhythmias as follows

1. The prevention and treatment of arrhythmias occurring after myocardial infarction.
2. Maintenance of normal rhythm following electroconversion e.g. atrial fibrillation, atrial flutter.
3. Persistent ventricular extrasystoles.
4. Control of arrhythmias following the use of digitalis or similar glycosides.
5. Suppression of arrhythmias during surgical procedures e.g. cardiac catheterisation.
6. The prevention of paroxysmal supraventricular tachycardia.
7. Other types of arrhythmias e.g. atrial extrasystoles, Wolff-Parkinson-White Syndrome.

4.2 Posology and method of administration

Posology: Oral

300 mg to 800mg daily in divided doses.

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)

Paediatric population

The safety and efficacy of disopyramide in children less than 18 years has not been established. Current available evidence is available in section 4.4, 5.1 and 5.2.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Disopyramide is contra-indicated in un-paced second or third degree atrioventricular block; bundle-branch block associated with first degree atrioventricular block; un-paced bifasicular block; pre-existing long QT syndromes; severe sinus node dysfunction and severe heart failure, unless secondary to cardiac arrhythmia. It is also contra-indicated in concomitant administration with other anti-arrhythmics or other drugs liable to provoke ventricular arrhythmias, especially Torsade de Pointes (see section 4.5). The sustained release formulation is contra-indicated in patients with renal or hepatic impairment.

4.4 Special warnings and precautions for use

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 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.

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

antiarrhythmic drugs should not be prescribed for the treatment of patients with asymptomatic ventricular premature contractions.

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.

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.

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.

Life-threatening and 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.

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.

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 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 only 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. The risk of hypoglycaemia, sometimes severe, occurs particularly in elderly or malnourished subjects, treated diabetics and patients with renal insufficiency or cardiac failure. Blood sugar levels should be monitored in all patients. Strict adherence to the dosing recommendations is advised. If hypoglycaemia occurs then treatment with disopyramide should be stopped.

Hypoglycaemia may be associated with interactions with drugs metabolised by hepatic CYP3A (see Section 4.5 Interactions with other medicinal products and other forms of interaction).

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 sections 4.4 renal/ hepatic insufficiency, 4.5 and 4.9)
- aggravation of myasthenia gravis
- cognitive disorders, especially in elderly patients (see also section 4.8).

Paediatric population: Paediatric patients with hepatic insufficiency may be at risk for increased exposures.

4.5 Interactions 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 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
- All macrolide antibiotics (e.g. erythromycin, clarithromycin, azithromycin etc)
- astemizole; cisapride; pentamidine; pimozone; sparfloxacin; terfenadine and thioridazine.

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.

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 orazole antifungal antibiotics) may therefore increase the serum levels of disopyramide. On the other hand, inducers of CYP3A (e.g. rifampicin and certain anticonvulsants such as phenytoin, primidone and phenobarbital) 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 can induce hypokalaemia such as : diuretics, amphotericin B, tetracosactide (corticotropin 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 sections 4.4 and 4.8).

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. Rythmodan 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: 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 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 hypokalemia with the associated use of antiarrhythmic drugs, in patients with severe structural heart disease 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, ventricular fibrillation, ventricular tachycardia and torsades de pointes.

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 effects (see also section 4.4):
 - urinary: dysuria; acute urinary retention, especially in prostatism
 - ocular: disorders of accommodation; diplopia
 - gastrointestinal: dry mouth; abdominal pain; nausea, vomiting, anorexia, diarrhoea; constipation
 - impotence
 - cognitive disorders
 - psychiatric disorders.
- Skin reactions: very rarely, rashes.
- Rarely: hypoglycaemia, sometimes severe (see Section 4.4 Special warnings and precautions for use). In some cases, severe hypoglycaemia resulted in coma.
- Very rarely: cholestatic jaundice, headache, dizzy sensation, neutropenia.
- Agranulocytosis.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms

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:

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

Management

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. Monitor vital signs and measure blood sugar, serum potassium, magnesium and calcium concentrations. Symptomatic therapeutic 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 counterpulsation and mechanically assisted ventilation,
- haemodialysis, haemofiltration or haemoperfusion with activated charcoal has been employed to lower the serum concentrations of the drug.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiarrhythmias, Class Ia

ATC code: C01BA03

It decreases membrane responsiveness, prolongs the effective refractory period (ERP) and slows automaticity in cells with augmented automaticity. Effective refractory period of the atrium is lengthened, ERP of the A-V node is shortened and conduction in accessory pathways is prolonged.

Disopyramide is a myocardial depressant and has anti-cholinergic effects.

Paediatric population

No controlled paediatric studies have been undertaken. One non-controlled study assessed the electrophysiologic effects of disopyramide in 14 children aged 7 months to 14 years with congenital heart disease. A single intravenous dose of disopyramide phosphate was administered (2 mg/kg, maximum 50 mg). Significant prolongations of the refractory periods of the atrium and the atrioventricular (AV) node, and also a significant prolongation of the His-ventricular (HV) interval were reported. No side effects were reported. In another study in 15 patients aged 9 days to 14 years with arrhythmia, oral disopyramide was started at 3 to 6 mg/kg and increased after 48h until the pre-dose plasma concentration of disopyramide attained >2 mg/L. The dose of disopyramide required to achieve a plasma concentration within the therapeutic range varied from 3 mg/kg to 36 mg/kg, with the highest requirement being found in the youngest patient. Seven out of fifteen subjects (46%) achieved arrhythmia control.

5.2 Pharmacokinetic properties

Elimination phase of plasma t_{1/2}: 5-8 hours. Increased in hepatic 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.

Paediatric population

In the paediatric population, a higher plasma clearance and shorter half-life were observed compared to adults. This could be explained by a higher metabolic clearance in the paediatric population.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Magnesium stearate

STA-RX 1500 (pregelatinised starch)

Talc.

Capsule shell:

Gelatin

Indigo carmine,

Iron oxide and

Titanium dioxide (E171)

6.2 Incompatibilities

Not known.

6.3 Shelf life

Glass Bottle : 36 months

PVC Blister : 36 months

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Glass Bottle containing 100 capsules

PVC Blister containing 84 capsules.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 04425/0607

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

17/06/2010

10 DATE OF REVISION OF THE TEXT

13/08/2019