DATA SHEET

1 RYTHMODAN® CAPSULES

Rythmodan 100mg capsules

Rythmodan 150mg# capsules

#Not marketed

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rythmodan 100mg and 150mg# capsules contain 100mg and 150mg of disopyramide respectively

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

100 mg capsules: green & beige, marked RY RL

150 mg# capsules: white, marked RY 150 in black.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Disopyramide is indicated for the treatment of symptomatic and/or life-threatening arrhythmias. Specific indications are as follows:

Disopyramide is indicated in the following symptomatic arrhythmias:

- atrial or ventricular extrasystoles
- treatment of atrial arrhythmias
- atrial fibrillation or flutter: preparation for cardioversion; substitution for cardioversion, when the latter is contraindicated or unfeasible; prevention of relapses following restoration of sinus rhythm

- prevention of attacks of paroxysmal tachycardia, Bouveret type, including Wolff-Parkinson-White syndrome
- prevention of relapses of paroxysmal ventricular tachycardia

4.2 DOSE AND METHOD OF ADMINISTRATION

The daily dose of RYTHMODAN capsules must be administered as no less than 3 equal divided doses.

Adults with Normal Hepatic and Renal Function:
Prevention or Curative Treatment of Symptomatic Arrhythmias
Initial treatment: 400 to 600 mg per day
Maintenance treatment: reached by progressively reducing the daily dose by 100 mg per day to reach a final dose of 300 to 400 mg per day on average.

Substitution Treatment for Cardioversion
When cardioversion is contraindicated or otherwise not feasible, the initial capsule dosage can be increased to 800 mg on the first day in 4 divided doses.

Preparation for cardioversion, after stopping digitalis
100 mg capsule on the previous evening
3 x 100 mg just before cardioversion in three doses at hourly intervals
100 mg capsule on the evening of cardioversion followed by the usual maintenance treatment from the next day onwards.

Adults with Renal Insufficiency:
The initial capsule dose should never be more than 200 mg.
Maintenance treatment should be given depending on the severity of the renal insufficiency.

Creatinine clearance	Unit dose	Dosing interval	Total daily dose
≥ 50 mL/min	100 mg	6 hours	400 mg
50 - 30 mL/min	100 mg	8 hours	300 mg
30 - 10 mL/min	100 mg	12 hours	200 mg
≤ 10 mL/min	100 mg	24 hours	100 mg

ECG and plasma concentrations should be monitored.

Adults with Hepatic Insufficiency (Cirrhosis):
The dosage of disopyramide should be reduced by 25% as a guide and then adjusted according to plasma concentrations and ECG monitoring in particular QRS and QTc duration.

4.3 CONTRAINDICATION

Cardiogenic shock

Second or third degree atrio-ventricular block (if no pace-maker is present)

Bundle branch block associated with first degree atrio-ventricular block

Double block (e.g. left posterior or anterior hemiblock and right bundle branch block)

Pre-existing long QT

Severe sinus node dysfunction

Cardiac insufficiency unless secondary to cardiac arrhythmia

Concomitant use with other antiarrhythmics, or other drugs liable to provoke ventricular arrhythmias or torsades de pointes (see Section 4.5).

Known hypersensitivity to disopyramide.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Myocardial Infarction

Antiarrhythmic drugs belonging to the class 1c were included in the Cardiac Arrhythmia Suppression Trial (CAST), a long term multicenter randomised, double-blind study in patients with asymptomatic non life threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously. An excess mortality or non-fatal cardiac arrest rate was seen in patients treated with antiarrhythmic drugs belonging to the class 1c, encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

While there are no comparable mortality trial data for other Class I antiarrhythmic agents post-myocardial infarction or in other clinical settings, meta-analyses of small scale clinical trials of these agents in similar populations suggest a trend towards increased mortality compared to placebo and no evidence of benefit.

All Class I antiarrhythmic agents share the capacity to produce slowing of conduction velocity which can promote tachycardias via re-entry mechanisms.

Therefore, the prophylactic use of Class I antiarrhythmic medicines following myocardial infarction is potentially hazardous. Indeed the use of these agents for other than life-threatening arrhythmias or severe symptoms due to arrhythmias is not recommended.

Antiarrhythmic drugs should not be prescribed for the treatment of patients with asymptomatic ventricular premature contractions, haemodynamically non-significant ventricular premature contractions.

In the event of aggravation of the pre-existing arrhythmia or emergence of a new type of arrhythmia, treatment with disopyramide should be reconsidered.

Heart failure/hypotension

Disopyramide may cause or worsen congestive heart failure or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily in patients with structural heart disease or inadequately compensated congestive heart failure. Disopyramide should not be used in patients with uncompensated or marginally compensated congestive heart failure or hypotension unless this heart failure or hypotension is secondary to cardiac arrhythmia. If hypotension occurs or congestive heart failure worsens, RYTHMODAN should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established.

Structural Heart Disease

Proarrhythmia and cardiac decompensation are a special risk associated with antiarrhythmic drugs. Special caution should be exercised. In patients with structural heart disease, the negative inotropic effects of disopyramide may be of concern; treatment should be given under strict supervision and cardiac function monitored. RYTHMODAN should not be administered to patients with structural heart disease and associated congestive heart failure unless the patient is adequately treated. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide, probably due to cardiodepressant mechanisms. Therefore, a loading dose of disopyramide should not be given to such patients and initial dosage and subsequent dosage adjustments should be made under close supervision.

Anticholinergic activity

Because of its anticholinergic properties, disopyramide should not be used in patients with urinary retention unless adequate overriding measures are taken; these consist of catheter drainage or operative relief.

Urinary retention may occur in patients of either sex as a consequence of disopyramide administration, but males with benign prostatic hypertrophy or prostatic adenoma are at particular risk.

Disopyramide should be avoided in patients with glaucoma.

In patients with a family history of glaucoma, intraocular pressure should be measured before initiating disopyramide therapy and controlled as necessary during treatment.

There is a risk of paralytic ileus occurring, especially in the elderly, and when disopyramide is taken with other anticholinergic medications or in situations where there is an increase in plasma levels of disopyramide, (see Sections 4.4, 4.5 and 4.8).

Disopyramide should be used with special care in patients with myasthenia gravis since its anticholinergic properties could precipitate a myasthenic crisis in such patients.

There is a risk of cognitive disorders in elderly patients that require medical attention. For other atropine-like effects, see the Adverse Effects section.

Heart Block

If an atrio-ventricular block or a double block occurs, treatment should be discontinued.

QRS Widening

QRS duration should be monitored. If significant widening (greater than 20%) of the QRS complex occurs, the medicine should be discontinued.

QT Prolongation

QT interval should be monitored. Prolongation of the QT interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the QT interval in response to quinidine may be at particular risk. If a QT prolongation of greater than 20 % is observed, the medicine should be discontinued.

Hypoglycaemia

Significant lowering of blood glucose values has been reported during disopyramide administration. The physician should be alert to this possibility, especially in aged or malnourished patients, diabetics, and patients with renal insufficiency. In these patients hypoglycaemia can be severe and as such, blood glucose levels should be monitored.

Hypokalaemia

Serum potassium must be monitored. Potassium abnormalities may induce arrhythmias. Antiarrhythmic medicines may be ineffective in patients with hypokalaemia. Undesirable cardiac effects of antiarrhythmics may be provoked by hyper- or hypo-kalaemia.

Before and during treatment with disopyramide, potassium imbalance should be looked for and corrected, particularly in case of treatment with potassium lowering diuretics or laxatives.

Renal Impairment

As more than 50 % of disopyramide is excreted in the urine unchanged, dosage should be reduced in patients with impaired renal function (see Section 4.2). The electrocardiogram should be carefully monitored for prolongation of PR and QT intervals, evidence of QRS widening or other signs of overdosage (see Section 4.9).

Hepatic Impairment

As hepatic impairment causes an increase in the plasma half-life of disopyramide, dosage should be reduced by 25%. The electrocardiogram should be carefully monitored for signs of overdosage (see Section 4.9).

Paediatric

RYTHMODAN is not approved for paediatric use.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Combinations of antiarrhythmic medicines are not well researched and their effect may be unpredictable. Thus, antiarrhythmic combination should be avoided except under certain circumstances, e.g. beta-blockers for angina pectoris; digoxin with a beta-blocker and verapamil for the control of atrial fibrillation, when defined as effective for an individual by specialised procedure.

Contraindicated associations:
Disopyramide should not be co-administered with the following medicines:

- Other antiarrhythmics (Vaughan Williams classification):
  - Class I: most drugs, including phenytoin.
  - Class II: beta-blocking medicines
  - Class III: amiodarone, bretylium, sotalol, ibutilide
  - Class IV: verapamil, diltiazem, lidoflazine, bepridil, prenylamine
- Medicines associated with the risk of torsades de pointe, such as:
  - Tricyclic and tetracyclic antidepressants.
  - Parenterally-administered erythromycin.
  - Vincamine
  - Sultopride

Not recommended:
The co-administration of disopyramide with some other medicines associated with a potential for torsades de pointe is not recommended. Such medicines include:

- Astemizole
- Cisapride
- Pentamidine
- Pimozide
- Sparfloxacin
- Terfenadine

Phosphodiesterase type 5 inhibitors
There is evidence that phosphodiesterase type 5 inhibitors may potentially lead to QT prolongation. Concomitant administration of phosphodiesterase 5 inhibitors with disopyramide may potentially enhance this QT prolongation effect and is not recommended.

There is some evidence that disopyramide is metabolised by CYP3A. Although human studies are not available, concomitant administration of significant inhibitors of this isozyme (eg certain macrolide antibiotics or azole antifungals) 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.

Stimulant laxatives are not recommended (see Section 4.4 – hypokalaemia)

Precautions for use:
Care is advised when the following medicines are used concomitantly with disopyramide:

- Hypokalemia-inducing medicines (see Section 4.4 - hypokalaemia) such as diuretics, amphotericin B, tetracosactide, gluco- and mineralo-corticoids.

To be considered:
Atropine and other anticholinergic medicines, including phenothiazines, may potentiate the atropine-like effects of disopyramide (see Section 4.4 and 4.8).

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.

Other interactions include the following:

- Roxithromycin: An in-vitro study has shown that roxithromycin can displace protein bound disopyramide; such an effect in vivo could result in increased serum levels of disopyramide.

If treatment with any of these drugs in necessary, cardiac function must be strictly monitored.

4.6 PREGNANCY AND LACTATION

Pregnancy
Category B2

Animal studies have not demonstrated any teratogenic effect and have revealed only minimal evidence of impaired fertility and a slightly lower weight in treated rats at the time of weaning. However, no controlled studies of disopyramide have been performed in pregnant women and experience with RYTHMODAN during pregnancy is limited. Disopyramide has been reported to stimulate contractions of the pregnant uterus and also passes into foetal circulation. Therefore, use of RYTHMODAN in women of childbearing potential requires that the benefits of therapy be weighed against its possible hazards to the mother and foetus.

Labour and delivery

It is not known whether use of disopyramide during labour or delivery has immediate or delayed adverse effects on the foetus, whether it prolongs the duration of labour, or increases the possibility of forceps delivery or other obstetrical intervention.

Breast-feeding
Disopyramide passes into breast milk. If use of the medicine is deemed essential, an alternative method of infant feeding should be instituted.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Some adverse reactions may impair the patient's ability to concentrate and react, and hence the ability to drive or operate machinery.

4.8 UNDESIRABLE EFFECTS

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 other antiarrhythmic medicines and/or a severe structural heart disease and/or prolongation of the QT interval.

Hypotension, QT interval prolongation, widening QRS, atrio-ventricular block, bundle branch block, bradycardia, sinus block, nodal rhythm dissociation and cardiac arrest have been reported. An occasional paradoxical ventricular tachycardia, evolving sometimes to fibrillation, has been observed.

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

The most common adverse effects which are dose dependent are associated with the anti-cholinergic properties of the medicine. These may be transitory, but may be persistent and can be severe. Urinary retention is the most serious anticholinergic effect.

The following adverse effects are reported in more than 10 % of patients:

Anticholinergic: dry mouth, acute urinary retention, especially in prostatism and constipation

Gastrointestinal: nausea, indigestion, vomiting, diarrhoea, flatulence, bad taste in the mouth, anorexia

The following adverse effects are reported in 1 to 10 % of patients:

Anticholinergic: blurred vision, dry eyes/nose/throat, urinary hesitation and frequency

Cardiovascular: hypotension with or without CHF, increased CHF, cardiac conduction disturbances, proarrhythmic effects, oedema, dyspnoea, cyanosis, chest pain

Dermatologic: skin reactions including pruritis, urticaria, morbilliform eruption, rash, photosensitisation.

General: dizziness, vertigo, drowsiness, profuse sweating

Other: raised SGOT levels

Isolated reports of anaphylactic-type reactions (e.g. urticaria, angioedema) possibly culminating in shock (reported in association with the I.V. injection)

The following adverse effects are reported in less than 1 % of patients:

Dysuria, headache, feeling of warmth, pallor, peripheral paraesthesia, fatigue, malaise, insomnia, confusion, transitory psychosis, elevated BUN, elevated creatinine, decreased haemoglobin/haematocrit, hypoglycaemia which can be severe (see Section 4.4), neutropenia, idiosyncratic reaction.

In a few instances, cholestatic jaundice has been reported. A definite causal relationship has not been established, however one case has been reported as probably related.

A high plasma concentration has been associated with impotence.

With intravenous administration, the occurrence of side effects, especially profuse sweating, was often associated with too rapid administration of the medicine.

Other adverse effects which have been reported include psychiatric disorders, cognitive disorders, agranulocytosis, ocular disturbances of accommodation and diplopia; and epigastralgia.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Symptoms

Toxic plasma levels are reflected by ECG abnormalities such as (a) marked prolongation of QT interval premonitory of other arrhythmias, in particular torsades de pointes, which can result in repeated syncope; (b) widening of the QRS complex; and (c) variable degrees of atrio-ventricular block.

The Clinical Signs of Overdose May Include paralytic ileus, bilateral mydriasis (suggestive); syncope, hypotension or shock; cardiac arrest due to intra-ventricular block or asystole; respiratory symptoms; and coma (with bilateral mydriasis) in cases of massive intoxication.

Treatment

Except for neostigmine or physostigmine, which may be used for treating anticholinergic effects, there is no specific antidote. Treatment of acute overdose should be carried out in an Intensive Care Unit under continuous cardiac monitoring.

Symptomatic therapeutic measures may include:

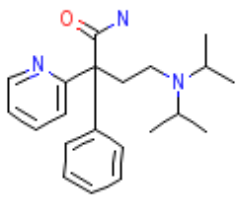
- administration of a cathartic followed by activated charcoal by mouth or stomach tube
- IV administration of isoprenaline and/or other vasopressors and/or positive inotropic agents
- if needed, infusion of lactate and/or magnesium, electro-systolic assistance, cardioversion, insertion of an intra-aortic balloon for counterpulsation, and mechanically assisted ventilation
- haemodialysis, haemofiltration or haemoperfusion with activated charcoal has been employed to lower serum concentration of the drug

Altering the urinary pH does not affect the plasma half-life or the amount of disopyramide excreted in the urine.

Contact the National Poisons Information Centre on 0800 POISON or 0800 764 766 for advice on management of overdosage.

5 PHARMACOLOGICAL PROPERTIES

Chemical Structure



Chemical Formula: $C_{21}H_{29}N_3O$

CAS Number 3737-09-5

5.1 PHARMACODYNAMIC PROPERTIES

Disopyramide (base) is 4-di-isopropylamino-2-phenyl-2-(2-pyridyl) butyramide. RYTHMODAN is a racemic mixture of the d- and l- isomers of disopyramide.

Disopyramide base (MW = 339.5) is a stable white powder, which is insoluble in water but soluble in dilute acid and organic solvents.

Site and Mode of Action

Disopyramide is a Class 1a antiarrhythmic agent (Vaughan Williams classification). It is a sodium channel blocker with membrane stabilising effect. It reduces automaticity in cardiac Purkinje fibres by depressing the slope of phase 4 diastolic depolarisation; slows conduction velocity in atria, A-V node, Purkinje fibres, and ventricular muscle by decreasing the rate of phase 0 depolarisation in these fibres; prolongs action potential duration and refractory period in atria, Purkinje fibres and ventricular muscle; depresses excitability of both atrial and ventricular muscle by its direct effect on the myocardium.

Electrophysiology
Disopyramide prolongs the effective refractory period of the atria and the ventricles. The effective refractory period of the atrio-ventricular node is either slightly shortened or unchanged. The relative refractory period of the His-Purkinje system is prolonged. Atrio-ventricular nodal conduction time is unchanged by RYTHMODAN. Conduction through the His-Purkinje system is unchanged or slightly delayed.

Haemodynamics
The haemodynamic effects vary according to the condition of the patient and the dose administered. The main changes induced by disopyramide are as follows: heart rate unchanged or slightly increased; cardiac output decreased by about 10%; peripheral resistance increased; slight, transient fall in blood pressure which is compensated for by increased peripheral resistance; left ventricular end diastolic pressure unchanged or increased; negative inotropic effect which can be marked in patients with depressed left ventricular function. Thus disopyramide produces a slight and transient myocardial depressant effect on the heart. This is more pronounced after intravenous administration than after oral administration.

Anticholinergic activity
Disopyramide possesses anticholinergic properties and has been shown to be up to 10% as potent as atropine in in vitro tests. The oral form has little or no effect on resting sinus rate. The anticholinergic side effects may affect the gastrointestinal and/or urogenital systems (see Section ~~4.~~4 and 4.8). These effects may be transitory or disappear upon reduction of dose.

5.2 PHARMACOKINETIC PROPERTIES

The bioavailability is 80 - 90% of the dose administered. After administration of 200 mg, the maximum plasma concentration is 2.1 - 3.5 mcg/mL, 0.5-3.0 hours after administration. In patients with renal insufficiency, the maximum concentration for the same dose is 3.6 ± 1.2 mcg/mL, 3.8 ± 2.2 hours after administration.

The plasma half-life is 4.4 to 8.2 hours in healthy volunteers and 17 ± 5 hours in patients with severe renal insufficiency.

The apparent volume of distribution is 42.0 ± 11.6L. In plasma, disopyramide is mainly bound in a saturable fashion to alpha-1 acid glycoprotein. The free fraction varies with the total concentrations of disopyramide and binding protein.

Excretion is both renal and in the faeces (80 - 90% and 10 - 20% respectively).

The amount excreted in urine in 24 hours is 1/3 of the oral dose ingested and comprises 70% free disopyramide and 30% of a pharmacologically active metabolite (mono N-dealkyl disopyramide). These percentages are reversed for faecal excretion.

5.3 PRECLINICAL SAFETY DATA

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Gelatin
Magnesium stearate
Maize starch
Pregelatinised maize starch (STA-RX 1500)
Purified talc
Titanium dioxide
Rythmodan 100mg capsules also contain iron oxide yellow and indigo carmine.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

5 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^{o}C

6.5 NATURE AND CONTENTS OF CONTAINER

100mg and 150mg[#] capsules:

Blister packs of 100 capsules.

[#]Not marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Only Medicine (S4)

8 SPONSOR

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street
Ellerslie, Auckland
Freecall: 0800 283 684

9 DATE OF FIRST APPROVAL

27 April 1973

10 DATE OF REVISION OF THE TEXT

31 May 2017

SUMMARY OF CHANGES

Section changed	Summary of new information
1,2,3, 6.5	Added reference #Not marketed for the 150mg strength capsules
2	Added excipient reference
4.3, 4.5, 4.8, 5.1	Updated section references
4.8	Added adverse event reporting details
5.3	Added 'Not applicable'
6.2	Added 'Not applicable'
6.3	Added shelf life as per TPDR
6.6	Added 'No special requirements for disposal'
8	Updated sponsor address and address freecall number
9	Added date of first approval as per TPDR
10	Updated revision of text to: xx xxxxxxx xxxx