1 NAME OF THE MEDICINAL PRODUCT

Rythmodan Retard 250mg Modified Release Tablets

Disopyramide Neon 250 mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 322.5 mg of the active substance Disopyramide Phosphate (equivalent to 250 mg base).

Excipients with known effects
Contains 30 mg of sucrose and 3.53 mg of glucose, anhydrous.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified release tablet.

Biconvex tablets and off-white in colour. One side has a break-line and is embossed 013 and E; the other side is embossed with the Roussel logo.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Properties:

Prevention and control of a wide variety of cardiac arrhythmias, probably by slowing conduction in the his-Purkinje system and by increasing the effective refractory period of the atria and ventricles.

Indications:

1. Maintenance of normal rhythm following conversion by parenteral drugs or electroconversion.
2. Prevention of arrhythmias after myocardial infarction.
3. Treatment of persistent ventricular and atrial extrasystoles, paroxysmal supra ventricular tachycardia, Wolff-Parkinson-White syndrome.
4. Suppression of arrhythmias during surgical procedures.

5. Control of arrhythmias following the use of digitalis or similar glycosides.

4.2 Posology and method of administration

Posology

Recommended dose for stabilised patients or those receiving disopyramide for the first time is one to one and a half tablets (250-375 mg) twice daily. Tablets should be swallowed and not crushed or chewed.

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).

Renal impairment
Disopyramide is contraindicated in cases of renal impairment (see section 4.3).

Hepatic impairment
Disopyramide is contraindicated in cases of hepatic impairment (see section 4.3)

Paediatric population
Disopyramide is contraindicated in children aged 0 to 18 years (see section 4.3).

Method of administration

Oral use.

4.3 Contraindications

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

Disopyramide is contraindicated in unpaced second- or third-degree atrioventricular block; bundle-branch block associated with first-degree atrioventricular block; unpaced bifascicular block; pre-existing long QT syndromes; severe sinus node dysfunction and severe heart failure, unless secondary to cardiac arrhythmia.

It is also contraindicated in concomitant administration with other antiarrhythmics or other drugs liable to provoke ventricular arrhythmias, especially Torsades de pointes (see section 4.5).

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

The sustained release formulation is contraindicated in children.

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 (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. 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 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 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 Torsades 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, disopyramide is contraindicated (see section 4.3).

Hepatic insufficiency: In hepatic insufficiency, disopyramide is contraindicated (see section 4.3).

Hepatic impairment causes an increase in the plasma half-life of disopyramide 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).

Atropine–like effects (see section 4.8): 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 and 4.5),
- aggravation of myasthenia gravis,
- cognitive disorders, especially in elderly patients.

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

Glucose
Patients with rare glucose-galactose malabsorption 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, e.g. 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 Torsades de pointes, such as
- tricyclic and tetracyclic antidepressants,
- all macrolide antibiotics (e.g. erythromycin, clarithromycin, azithromycin etc.),
- astemizole; cisapride; pentamidine; sparfloxacin; terfenadine; pimozide 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. macrolide or azole 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 that 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 Fertility, pregnancy and lactation

Pregnancy
Although disopyramide 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.

Breast-feeding
No data for disopyramide, 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

The frequencies of possible undesirable effects listed below are currently defined as:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000
Not known	cannot be estimated from the available data

Cardiac disorders:

Not known:
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 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 section 4.4):
  Not known:
  - Psychiatric disorders
  - Nervous system disorders: cognitive disorders; myasthenia gravis aggravated
  - Eyes disorders: disorders of accommodation; diplopia; ocular hypertension in patients with glaucoma
  - Gastrointestinal disorders: dry mouth; abdominal pain; nausea; vomiting; anorexia; diarrhoea; constipation; paralytic ileus especially in the elderly
  - Renal and urinary disorders: dysuria; acute urinary retention, especially in prostatism
  - Reproductive system and breast disorders: impotence

- Blood and lymphatic disorders
  Very rare: neutropenia,
  Not known: agranulocytosis

- Metabolism and nutrition disorders
  Rare: hypoglycaemia, sometimes severe (see section 4.4). In some cases, severe hypoglycaemia resulted in coma.

- Nervous system disorders
  Very rare: headache, dizzy sensation

- Hepatobiliary disorder

Very rare: cholestatic jaundice

- Skin and subcutaneous tissue disorders
  Very rare: rashes

Reporting of suspected adverse reactions
Reporting 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 concentration of the drug.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy; Antiarrhythmics, Class Ia, ATC code: C01BA03

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

The dissolution characteristics of disopyramide are designed to release 250 mg disopyramide over 12 hours. The dissolution profile is matched to the drug half-life of 6 - 8 hours with good initial 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

Glyceryl monostearate

Sucrose

Povidone

Magnesium stearate

Film coating:

Hydroxypropyl methylcellulose

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 25ºC.

6.5 Nature and contents of container

PVC/PVDC/Aluminium Blister containing 56, 60 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Neon Healthcare Ltd.
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John Tate Road
Hertford
SG13 7NN
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 45043/0030

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