Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kinidin Durules 200 mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains quinidine bisulphate tetrahydrate equivalent to 200 mg quinidine sulphate dihydrate.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-Coated Prolonged release Tablets
Kinidin Durules 200 mg prolonged-release tablets are film-coated, white to off-white, oval tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an antiarrhythmic agent for the maintenance of sinus rhythm following electrical conversion of atrial fibrillation. Suppression of supraventricular and ventricular tachyarrhythmias.

4.2 Posology and method of administration

Initiation of treatment, as with other antiarrhythmic agents used to treat life-threatening ventricular arrhythmias, should be carried out in hospital.

Dosage is adjusted according to individual patient requirements. The quinidine dose should preferably be established by determination of the serum concentration after about one week of treatment. The therapeutic plasma concentration range is 1-6 mg/l (3-18 micromol/l). The QT-time should be checked before and during treatment.

Normal dose is 2-5 tablets (0.4-1.0g) morning and evening. The normal dose for maintenance treatment after conversion of atrial fibrillation is 3 tablets (0.6g) morning and evening.

Kinidin Durules 200 mg Prolonged-Release Tablets must not be chewed or crushed. They should be swallowed whole with half a glass of water.

Impaired Renal Function
No dose adjustment is needed. Among patients with advanced renal disease, quinidine clearance is only modestly decreased. Thus, dosage requirements in these patients are similar to those in other patients.

Impaired Hepatic Function
Reduced dosage should be considered for patients with hepatic impairment. The quinidine dose should preferably be established by determination of the serum concentration. The therapeutic plasma concentration range is 1-6 mg/l (3-18 micromol/l).

Elderly
Reduced dosage should be considered.

Children
There is no documented experience of quinidine use in children.

4.3 Contraindications

Known hypersensitivity to quinidine, quinine, or any of the excipients.
Complete AV block with an AV nodal or idioventricular pacemaker. Second-degree AV block in the absence of a pacemaker. Digitalis intoxication. Intraventricular conduction defects. Prolonged QT interval. Aberrant impulses or abnormal rhythms due to escape mechanisms should not be treated with quinidine. Previous or current thrombocytopenia. Myasthenia gravis.

4.4 Special warnings and precautions for use

The patient should be observed after the first dose with special attention to hypersensitivity reactions. Quinidine should be administered with caution to patients with prolonged AV-conduction, sustained decompensation, cardiogenic shock, hypotension, bradycardia or disturbed potassium balance.

This product should not be used in the treatment of atrial fibrillation of hyperthyroidism, prior to surgical resection of the gland.

Hypokalaemia should be corrected before quinidine treatment is started. Heart failure, myocarditis or severe myocardial damage also requires caution.

Caution is indicated in combined therapy with other Class 1 antiarrhythmic drugs, beta-blockers and digitalis glycosides (see further interaction with digoxin and digitoxin).

In patients treated with digoxin, the digoxin dosage should be halved if quinidine is given in addition.

Like other antiarrhythmic drugs quinidine may worsen arrhythmias.

At toxic quinidine concentrations, and in some patients even at therapeutic levels, the QT-interval may be considerably prolonged, which increases the risk of ventricular tachycardia, often of the torsades de pointes type and in some cases also ventricular fibrillation.

Kinidin Durules Prolonged – release Tablets should be used with caution in the presence of obstructive changes in the digestive tract, especially in patients with constriction of the oesophagus, when there is a potential risk of oesophageal complications.

4.5 Interaction with other medicinal products and other forms of interaction

It is possible to explain observed drug-drug interactions or even in certain cases predict the potential for drug-drug interactions based on the site of metabolism/excretion or other pharmacological effects of a drug.

Quinidine is completely metabolised.

<u>Potential for influence of quinidine on the plasma levels/clinical effect of other drugs</u>

Quinidine is metabolised by cytochrome P4503A4 (CYP3A4) and this has the potential to inhibit the mechanism of other drugs metabolised by this enzyme, resulting in increased plasma levels of such drugs. This has been reported for coumarin derivates, such as warfarin and for nifedipine.

Quinidine has also been shown to very potently inhibit another CYP isoform, CYP2D6. Consequently, quinidine has the potential to inhibit the mechanism of other drugs metabolised by this enzyme, resulting in increased plasma levels of such drugs. On concomitant administration of quinidine, elevated plasma levels of other drugs have been reported with beta-blockers, such as metoprolol, propranolol and timolol, phenothiazines such as thioridazine and perphenazine, serotonin reuptake inhibitors such as fluoxetine and norfluoxetine, opiates such as codeine and dextromethorphan, antipsychotics such as haloperidol and zuclopenthixol, cardiac agents such as flecainide, mexiletine and propafenone,

tricyclic antidepressant drugs such as amitriptyline and nortriptyline or the antidepressant mianserin.

Quinidine will also inhibit the metabolism of desipramine, imipramine and desmethylclomipramine in rapid hydroxylators, resulting in increased plasma concentrations, and since they have additive antiarrhythmic properties such combinations should be avoided.

In addition, quinidine has been reported to increase plasma levels of digitoxin, digoxin and procainamide. Part of the explanation for the effect on digoxin and procainamide is a decreased renal tubular secretion of this drug caused by quinidine.

Furthermore, concomitant administration of quinidine and atenolol has resulted in orthostatic hypotension.

This list of drugs is not exhaustive and other drugs acting with similar mechanisms to those above should be considered to have the potential for an interaction with quinidine.

Potential for influence of other drugs in the plasma levels/clinical effect of quinidine

Drugs which are substrates, inhibitors or inducers of cytochrome CYP3A4 will have the potential to influence the metabolism of quinidine, resulting in altered quinidine plasma levels and hence modifying the clinical effect of quinidine.

Concomitant administration of drugs which will reduce quinidine plasma levels include CYP1A4 inducers; such as rifampicin, phenytoin, phenobarbital and carbamazepine. Quinidine plasma concentration may be reduced to a sub-therapeutic level if normal dosage is maintained.

Concomitant administration of drugs which will reduce quinidine plasma levels include CYP3A4 inducers; such as macrolide antibiotics, for example erythromycin, clarithromycin and troleandomycin, azole antifungals, for example ketoconazole, fluconazole, itraconazole and miconazole, and protease inhibitors such as ritonavir.

Similarly concomitant administration of drugs which will increase quinidine plasma levels include the substrates amiodarone and calcium channel blockers, such as diltiazem, and verapamil. The interaction between nifedipine and quinidine is complex, and conversely simultaneous administration of nifedipine has been reported to reduce plasma quinidine levels. Appropriate dosage adjustment and ECG monitoring should be carried out when these drugs are added or discontinued. During quinidine therapy, a 30-50% change in quinidine dosage may be required to avoid systemic toxicity or in the case of nifedipine lack of efficacy.

Furthermore, plasma levels have been reported to increase during concomitant administration with cimetidine, which has an unspecific inhibiting effect on CYP (including CYP3A4) mediated metabolism.

This list is not exhaustive and other drugs acting with similar mechanisms to those above should be considered to have the potential for an interaction with quinidine.

4.6 Pregnancy and lactation

Data about the use of quinidine during a limited number of pregnancies does not show a higher risk of malformations. There are no data from animal experiments. Quinidine passes through the placenta. The foetal and maternal blood levels are nearly the same. At therapeutic dosages, oxytocic effects of quinidine are reported rarely. The appearance of pharmacological effects in the foetus cannot be excluded. When prescribed to pregnant women, the benefit for the mother should be considered against the possible risk for the child.

Quinidine is excreted in breast milk but not likely to affect the infant when the therapeutic doses are used.

4.7 Effects on ability to drive and use machines

Patients should know how they react to quinidine before they drive or use machines.

4.8 Undesirable effects

Gastrointestinal adverse reactions are frequent and occur in approximately 30% of the patients.

The following definitions of frequencies are used:
Common ≥1/100
Uncommon ≥1/1000 and <1/100
Rare <1/1000

Blood and lymphatic system disorders
Rare: Thrombocytopenia, pancytopenia, agranulocytosis.

Nervous system disorders
Uncommon: Signs of cinchonism, e.g. tinnitus, blurred vision, headache and dizziness.

Cardiac disorders
Common: Arrhythmias such as ventricular tachycardia, mostly of the torsades de pointes type or ventricular fibrillation.
Uncommon: Bradycardia, cardiac arrest.

Vascular disorders
Uncommon: Hypotension.

Gastrointestinal disorders
Common: Diarrhoea, nausea and vomiting.

Hepatobiliary disorders
Rare: Hepatitis.

Skin and subcutaneous tissue disorders
Uncommon: Urticaria, skin rash.
Rare: Photosensitization, vasculitis, toxic epidermal necrolysis (TEN).

Musculoskeletal, connective tissue and bone disorders
Rare: Myalgia, arthralgia, lupus erythematosus-like syndrome.

General disorders
Rare: Fever, fatigue.

4.9 Overdose

Symptoms

Cinchonism (blurred vision, deafness, weakness, vertigo, tinnitus, headache) nausea and vomiting, also occur in varying degrees. Metabolic acidosis and hypokalaemia may complicate severe poisoning.

Poisoning due to an overdose of Kinidin Durules 200 mg Prolonged-release Tablets may lead to widening of the QRS complex and prolongation of the QT interval, atrioventricular block, extrasystoles, sinoatrial block or arrest, asystole, paroxysmal ventricular tachycardia, intraventricular block, flutter or ventricular fibrillation, myocardial depression, severe hypotension and cardiac arrest.

Serious hypersensitivity reactions are manifested by respiratory embarrassment or vascular collapse. Sedation and convulsions may also occur.
Lethal outcome has been reported after 4-8g.

Management

Discontinue medication at the first sign of toxicity.

Further absorption may be prevented by induction of vomiting or gastric lavage, or administration of water, milk or activated charcoal if ingestion is recent.

Treatment should include close monitoring of cardiovascular, respiratory and renal function, electrolytes and continuous ECG monitoring.

Cardiovascular complications should be treated symptomatically, which may require the use of sympathomimetic agents (e.g. noradrenaline, norepinephrine, metaraminol), or inotropic agents (e.g. dopamine, dobutamine). Temporary pacing may be required for AV block. Glucagon may be used to treat hypotension, and intravenous sodium bicarbonate to correct acidosis and intravenous diazepam for convulsions.

Quinidine and its metabolites cannot be removed effectively by peritoneal or haemodialysis, or charcoal column haemoperfusion but repeated oral administration of activated charcoal may enhance elimination. Forced acid diuresis is not recommended.

As Kinidin Durules 200 mg Prolonged-release tablets is an extended release preparation, treatment of overdosage may be required for a longer period.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cardiac antiarrhythmics, class la quinidine.
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Quinidine reduces the excitability, automaticity and conduction velocity in the atrium, AV-node and ventricle and increases the duration of the action potential and the effective refractory period. These effects are closely related to the blockade of the 'fast sodium channels' in the cell membranes, resulting in a reduced rate of the rise of action potential and thus a slower conduction and reduced automaticity in the Purkinje fibres.

The effect is considerably diminished when the extra-cellular potassium concentration is reduced and enhanced when it is increased.

The direct electrophysiological effects are modified by a relatively pronounced anticholinergic effect dominating particularly at lower plasma concentrations.

5.2 Pharmacokinetic properties

Oral bioavailability of quinidine is 70-80%, the absorption is not influenced by concomitant intake of food. Plasma protein binding is 70%-95%. Half life in the elimination phase is approximately 6 hours and the dose is almost entirely excreted in the urine, 10-20% as unchanged drug. Alkaline urine prolongs the elimination time.

The Durules formulation provides gradual release of active substances, thereby reducing the plasma concentration peaks. The absorption phase is prolonged compared to ordinary tablets and more constant and prolonged effect is achieved, reducing the number of doses needed per day. The peak serum concentration is reached 4 hours after intake of Kinidin Durules 200 mg Prolonged-release Tablets.

5.3 Preclinical safety data

Quinidine bisulphate is a well established active ingredient.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Macrogol 6000
Paraffin
Polyvinyl chloride
Polyvinyl acetate
Magnesium stearate
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Blister Strip - 5 years.
Securitainer - 2 years.

6.4 Special precautions for storage

Blister Strip - Do not store above 25°C.
Securitainer - Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Blister Strip of thermoformed PVC (10 tablets per strip) 100 tablets.

High density polyethylene [HDPE] securitainer bottle with a tight fitting polypropylene screwcap. 100 and 250 tablets.

Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
600 Capability Green
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8 MARKETING AUTHORISATION NUMBER

PA 970/43/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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