SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Disopyramide Phosphate 100 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 128.90 mg Disopyramide Phosphate equivalent to Disopyramide 100 mg

Excipient with known effect
Each capsule contains 113.1 mg lactose
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Disopyramide 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, Wolf-Parkinson-White Syndrome.

4.2 Posology and method of administration

Adults
300-800mg in divided doses adjusted according to the response of the patient.

Heart Failure

In determining the intervals between administration of Disopyramide capsules it should be borne in mind that whilst the elimination half-life in normal volunteers is approximately seven hours, in patients with heart failure, half-life values of 12 hours or more have been recorded.

Elderly
A dose reduction should be considered in the elderly (especially elderly non-smokers) with reduced renal and hepatic function (see section 4.4).

A reduced dosage, preferably accompanied by assay of Disopyramide plasma levels in cases of severe renal failure (creatinine clearance <8ml/min) is recommended. The following table may be helpful as a guide.

Creatinine Clearance (ml/min)	*Dosage 100 or 150mg capsules*
Normal	Normal Dosage
20 - 60	100mg 8 hourly or 150mg 12 hourly
8 - 20	100mg 12 hourly
< 8	150mg daily

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.

Posology
For oral administration only. The capsules should be swallowed whole and not chewed or opened.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Disopyramide is contra-indicated in patients with un-paced second or third degree atrioventricular block, bundle-branch block associated with first degree atrioventricular block; un-paced bifascicular block, and severe sinus node disease if no pacemaker is present, cardiogenic shock and severe uncompensated heart failure, unless of secondary to cardiac arrhythmia.
Disopyramide is also contra-indicated in patients with pre-existing long QT syndromes. Concomitant administration with other antiarrhythmics or drugs liable to provoke ventricular arrhythmias, especially Torsades de Pointes (see section 4.5).

4.4 Special warnings and precautions for use

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 non life-threatening arrhythmia; the expected benefits should be balanced against the 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 is secondary to cardiac arrhythmia. If dispoyramide 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.

There have been reports of ventricular tachycardia or ventricular fibrillation or torsade de pointes in patients receiving Disopyramide. These have been usually, but not always, 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 ECG 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. Accordingly the need for prior digitalisation should be considered.

Owing to its negative inotrophic 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 initiating treatment with Disopyramide.

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 occurs during treatment, the use of Disopyramide should be reviewed.

The occurrence of hypotension following Disopyramide administration, which has been observed especially in patients with cardiomyopathy or inadequately compensated congestive heart failure, requires prompt discontinuation of the drug. Any resumption of therapy should be a lower dose with close patient monitoring.

Disopyramide should be used with caution in treatment of digitalis intoxication.

Care should be taken when prescribing Disopyramide with bundle branch block as the effect of Disopyramide in this condition is unpredictable. If first degree heart block develops in a patient receiving Disopyramide, dosage should be reduced and may require discontinuation if the block persists.

Since Disopyramide is eliminated predominantly by glomerular filtration the dose administered to patients with significant renal impairment may require adjustment.

Hepatic insufficiency
Hepatic impairment causes an increase in the plasma half-life of Disopyramide and a reduced dosage may be required.

Potassium imbalance
Antiarrhythmic drugs may be hazardous in patients with potassium imbalance, as potassium abnormalities can induce arrhythmia. Disopyramide should be used with caution in patients receiving concurrent therapy with diuretics or stimulant laxatives, as these are likely to give rise to hypokalaemia. Potassium levels should be checked regularly.

Renal insufficiency
In renal insufficiency, the dosage of Disopyramide should be reduced by adjusting the interval between administrations.

Atropine-like effects
Due to its anticholinergic properties, 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 in patients with myasthenia gravis or
- cognitive disorders, especially in the elderly (see section 4.8).

These targets of patients may be unsuitable for Disopyramide therapy.

Hypoglycaemia
Hypoglycaemia, sometimes severe, has been reported in association with Disopyramide administration, particularly in elderly and malnourished patients, in patients with impaired renal or hepatic function, cardiac failure or

other conditions predisposing to disturbance of gluco-regulatory mechanisms. Blood sugar levels should be monitored in all patients and strict adherence to the dosing recommendations is advised. Treatment with Disopyramide should be discontinued if hypoglycaemia occurs.

Hypoglycaemia may be associated with interactions with drugs metabolised by hepatic CYP3A (see section 4.5).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

4.5 Interaction with other medicinal products and other forms of interaction

Combination with other antiarrhythmic drugs
The use of Disopyramide in combination with other negative inotrophic drugs such as beta-adrenoceptor blockers or the calcium channel blocker verapamil may result in summation of negative inotrophic effects, especially in patients with AV nodal or bundle branch conduction defects. Thus, antiarrhythmic combinations should be avoided except when deemed effective for an individual e. g. beta-blockers for angina pectoris, digoxin with beta-blocker and/or verapamil for the control of atrial fibrillation. Disopyramide may also summate with other class 1 anti-arrhythmic agents such as lidocaine, phenytoin and procainamide.

Interaction with drugs associated with risk of Torsade de Pointes
There is an increased risk of cardiac arrhythmias if Disopyramide is given concurrently with the following medications:
Tricyclic and tetracyclic antidepressants, all macrolides antibiotics (e.g. erythromycin, clarithromycin, azithromycin etc) antibiotics quinupristin or dalfopristin, antihistamines terfenadine and mizolastine, antipsychotics pimozide, sertindole or thioridazine, ritonavir, sotalol, verapamil, cisapride, tropisetron, astemizole, pentamidine, sparfloxacin, halofantrine and amiodarone.

The concomitant use of these medications with Disopyramide should be avoided.

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.

Plasma concentration of Disopyramide is reduced by the antiepileptic drugs phenobarbital, phenytoin and primidone and also by the antibacterial

rifampicin. However it is increased by erythromycin and possibly by clarithromycin.

There is some evidence to suggest the Disopyramide is metabolised by hepatic CYP3A. Concomitant administration of inhibitors of this isozyme (e.g. certain macrolide or azole antifungal antibiotics) may therefore increase the serum levels of Disopyramide, leading to toxicity. Conversely inducers of CYP3A (e.g. certain anticonvulsants and rifampicin) may reduce Disopyramide, and increase MN–disopyramide serum levels. Since the effects are not predictable, the combinations should be avoided.

When prescribing a drug metabolised by CYP3A e.g. theophylline, Warfarin, ciclosporin A and HIV protease inhibitors such as ritonavir, indinavir or saquinavir, it should be remembered that Disopyramide may also be a substrate of this isozyme. Therefore competitive inhibition of metabolism may occur, leading to increased serum levels of one or other of the drugs involved.

Interactions with hypokalaemia inducing drugs
Risk of cardiac toxicity of Disopyramide is increased when hypokalaemia occurs with acetazolamide, loop diuretics and thiazides. Amphotericin B, tetracosactrin (corticotrophrin analogue) gluco and mineralocorticoids may reduce the action of the drug or potentiate arrhythmia.

Other drugs that have the potential to lower potassium levels e.g. laxatives are also not recommended for concomitant use.

Other drug interactions
Atropine and other anticholinergenic drugs, including phenothiazines, may induce 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 in pregnancy if the benefits clearly outweigh the possible risks to the mother and foetus.

Breast-feeding
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 clinicians judgement, it is essential for the welfare of the patient. The infant should be closely supervised, particularly for anti-cholinergic 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 side effects e.g. blurred vision, may affect the patient's ability to concentrate and react, and hence the ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Disopyramide is usually well tolerated, however the following undesirable effects may occur.

Cardiac

There have been reports of ventricular tachycardia, ventricular fibrillation or Torsade de Pointes in patients receiving Disopyramide. These have been usually, but not always, associated with significant widening of the QRS complex, prolonged QT interval or other inter-cardiac conduction abnormalities such as atrioventricular and bunch bundle block. Bradycardia and sinus block have also been reported. The occurrence of hypotension following Disopyramide administration, which has been observed especially in patients with cardiomyopathy or inadequately compensated congestive heart failure, requires prompt discontinuation of the drug. Any resumption of therapy should be at a lower dose with close patient monitoring.

As with all antiarrhythmic drugs, there is a small possibility that Disopyramide may worsen or even provoke arrhythmia. This risk is increased in the presence of hypokalaemia, with the concomitant use of other antiarrhythmic drugs, in patients with severe structural heart disease or prolongation of the QT interval.

Episodes of severe heart failure or cardiogenic shock have also been described in patients with severe structural heart disease. The resulting low cardiac output can cause hypotension, renal insufficiency and/or acute hepatic ischaemia.

Other side-effects

- 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). In some cases, severe hypoglycaemia resulted in coma.

- Very rarely: cholestatic jaundice, headache, dizzy sensation, neutropenia.

- Agranulocytosis.

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

Overdosage may lead to cardiac arrest or atrio-ventricular block or to disorders of ventricular excitability leading to terminal ventricular fibrillation.

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

counterpulsion and mechanically assisted ventilation,
- haemodialysis, haemofiltration or haemoperfusion with activated charcoal has been employed to lower the serum concentrations of the drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiarrhythmics, class Ia, ATC code: C01BA03

Disopyramide is a class 1A anti-arrhythmic agent with a depressant action on the heart. 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. It also has antimuscarnic and negative inotrophic properties.

Disopyramide is mainly used for the prevention and treatment of ventricular and supra ventricular arrhythmias.

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

Absorption
Disopyramide is readily and almost completely absorbed from the gastro-intestinal tract, peak plasma concentrations being attained about 0.5 to 3 hours after oral administration.

Distribution
Disopyramide is widely distributed throughout the body and is extensively bound to plasma proteins between 50 – 60%; there is some disagreement as to factors, including dosage, which may influence protein binding. Estimations

of the plasma half-life of Disopyramide range from about 5 to 8 hours and is increased in hepatic impairment, cardiac and hepatic disease. The therapeutic effort of Disopyramide has been correlated with plasma concentrations in the range of about 2 to 6µg per ml.

Metabolism
Approximately 25% of a dose metabolised to a mono-N-dealkylated derivative. Additional 10% as other metabolites.

Elimination
75% unchanged drug via urine, remainder in faeces mono-N-dealkylated metabolite 25% in urine, 64% via faeces.

Disopyramide crosses the placenta barrier and animal studies have indicated that it is excreted in breast milk.

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

There are no preclinical safety data of relevance to the prescriber which are additional to those already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule:
Lactose
Maize Starch
Povidone K29/32
Purified Talc
Magnesium Stearate

Capsule Shell:
Red Iron Oxide (E172)
Yellow Iron Oxide (E172)
Titanium Dioxide (E171)
Gelatin

Printing Ink (10A1 Black)
Shellac
Iron oxide black (E172)
Propylene Glycol

Ammonium Hydroxide

6.2. Incompatibilities

None known.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store in a dry place below 25 °C.

6.5. Nature and contents of container

Polypropylene container with polyethylene cap with optional use of a polyethylene ullage filler in packs of 28, 30, 56, 60, 84, 90, 100, 112, 120, 168, 500 or 1000 capsules.

PVC/ Aluminium foil blister in packs of 28, 30, 56, 60, 84, 90, 100, 112, 120, 168, 500 or 1000 capsules.

6.6. Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan
Station Close
Potters Bar
Herts
EN6 1TL

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0026

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