Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amiodarone Hydrochloride 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg amiodarone hydrochloride.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White to off white, circular, biconvex tablet engraved 200 with action potential on one side and scored on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment should be initiated and normally monitored only under hospital or specialist supervision. Amiodarone is indicated for the treatment of severe rhythm disorders only when not responding to other therapies or when other treatments cannot be used.

Tachyarrhythmias associated with Wolff-Parkinson-White syndrome.

Atrial flutter and fibrillation when other drugs cannot be used.

All types of tachyarrhythmias including supraventricular, nodal and ventricular tachycardias, ventricular fibrillation, when other drugs cannot be used.

Amiodarone is indicated for the prevention of ventricular arrhythmias in high-risk patients following myocardial infarction or in patients with clinical signs of congestive cardiac failure and/or Left Ventricular Ejection Fraction (LVEF) less than 40% who are receiving appropriate cardiac failure treatment which includes Angiotensin Converting Enzyme (ACE)-inhibitors. The minimum effective dose must be used and treatment must be initiated and used only under hospital/specialist supervision.

4.2 Posology and method of administration

Amiodarone Tablets are for oral administration.

Adults
It is particularly important that the minimum effective dose be used. In all cases the patient's management must be judged on the individual response and well being. The following dosage regimen is generally effective.

Initial Stabilisation
Treatment should be started with 200mg, three times a day and may be continued for 1 week. The dosage should then be reduced to 200mg, twice daily for a further week.

Maintenance
After the initial period the dosage should be reduced to 200mg daily, or less if appropriate. Rarely, the patient may

require a higher maintenance dose. The scored 100mg tablet should be used to titrate the minimum dosage required to maintain control of the arrhythmia. The maintenance dose should be regularly reviewed, especially where this exceeds 200mg daily.

General Considerations
Initial dosing
A high dose is needed in order to achieve adequate tissue levels rapidly.

Maintenance
Too high a dose during maintenance therapy can cause side effects which are believed to be related to high tissue levels of amiodarone and its metabolites.

Amiodarone is strongly protein bound and has an average plasma half life of 50 days (reported range 20-100 days). It follows that sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dosage. In patients with potentially lethal arrhythmias the long half life is a valuable safeguard as omission of occasional doses does not significantly influence the overall therapeutic effect.

It is particularly important that the minimum effective dosage is used and the patient is monitored regularly to detect the clinical features of excess amiodarone dosage. Therapy may then be adjusted accordingly.

Dosage reduction/withdrawal
Side effects slowly disappear as the tissue levels fall. Following drug withdrawal, residual tissue-bound amiodarone may protect the patient for up to a month. However, the likelihood of recurrence of arrhythmia during this period should be considered.

Elderly
As with all patients it is important that the minimum effective dose is used. Whilst there is no evidence that dosage requirements are different for this group of patients they may be more susceptible to bradycardia and conduction defects if too high a dose is employed. Particular attention should be paid to monitoring thyroid function. (*See sections 4.3, 4.4 and 4.8).*

4.3 Contraindications

Sinus bradycardia and sino-atrial heart block. In patients with severe conduction disturbances (high grade AV block, bifascicular or trifascicular block) or sinus node disease, amiodarone should be used only in conjunction with a pacemaker.
Evidence or history of thyroid dysfunction.

Known hypersensitivity to iodine or to amiodarone or to any of the excipients. (One 200mg tablets contains approximately 75mg iodine).

Concomitant administration of amiodarone with drugs which may induce Torsades de Pointes (*see section 4.5).*
Pregnancy except in exceptional circumstances (see section 4.6)

Lactation (*see section 4.6).*

4.4 Special warnings and precautions for use

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

Paediatric patients:
The safety and efficacy of amiodarone in paediatric patients have not been established.

Cardiac disorders *(see section 4.8):* Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these

circumstances, amiodarone treatment should be withdrawn. If necessary beta-adrenostimulants or glucagon may be given. Because of the long half-life of amiodarone, if bradycardia is severe and symptomatic the insertion of a pacemaker should be considered.

The pharmacological action of amiodarone induces ECG changes: QT prolongation (related to prolonged repolarisation) with the possible development of U-waves and deformed T-waves; these changes do not reflect toxicity.

In the elderly, heart rate may decrease markedly.

Treatment should be discontinued in case of onset of 2nd and 3rd degree A-V block, sino-atrial block or bifascicular block.

Amiodarone has a low pro-arrhythmic effect. Onsets of new arrhythmias or worsening of treated arrhythmias, sometimes fatal, have been reported. It is important, but difficult, to differentiate a lack of efficacy of the drug from a proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects generally occur in the context of drug interactions and / or electrolytic disorders (*see sections 4.5. and 4.8*).

Hyperthyroidism (*see sections 4.4 and 4.8*):
Hyperthyroidism may occur during amiodarone treatment, or, up to several months after discontinuation. Clinical features, such as weight loss, asthenia, restlessness, increase in heart rate, onset of arrhythmia, angina, congestive heart failure should alert the physician. The diagnosis is supported by a decrease in serum ultrasensitive TSH (usTSH) level, elevated T_3 and a reduced TSH response to thyrotropin releasing hormone (TRH). Elevation of reverse T_3 (rT_3) may also be found.

In the case of hyperthyroidism, therapy should be withdrawn. Clinical recovery usually occurs within a few months, although severe cases, sometimes resulting in fatalities, have been reported. Clinical recovery precedes the normalisation of thyroid function tests.

Courses of anti-thyroid drugs have been used for the treatment of severe thyroid hyperactivity; large doses may be required initially. These may not always be effective and concomitant high dose corticosteroid therapy (e.g. 1mg/kg prednisolone) may be required for several weeks.

Pulmonary disorders (*see section 4.8*):
Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity (hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonitis). Presenting features can include dyspnoea (which may be severe and unexplained by the current cardiac status), non-productive cough and deterioration in general health (fatigue, weight loss and fever). The onset is usually slow but may be rapidly progressive. Whilst the majority of cases have been reported with long term therapy, a few have occurred soon after starting treatment

Patients should be carefully evaluated clinically and consideration given to chest X-ray before starting therapy. During treatment, if pulmonary toxicity is suspected, this should be repeated and associated with lung function testing including where possible measurement of transfer factor. Initial radiological changes may be difficult to distinguish from pulmonary venous congestion. Pulmonary toxicity has usually been reversible following early withdrawal of amiodarone therapy, with or without corticosteroid therapy. Clinical symptoms often resolve within a few weeks followed by slower radiological and lung function improvement. Some patients can deteriorate despite discontinuing amiodarone.

Liver disorders (*see section 4.8*):
Amiodarone may be associated with a variety of hepatic effects, including cirrhosis, hepatitis, jaundice and hepatic failure. Some fatalities have been reported, mainly following long-term therapy, although rarely they have occurred soon after starting treatment particularly after intravenous amiodarone. It is advisable to monitor liver function particularly transaminases before treatment and six monthly thereafter.

At the beginning of therapy, elevation of serum transaminases which can be in isolation (1.5 to 3 times normal) may occur. These may return to normal with dose reduction, or sometimes spontaneously.
Isolated cases of acute liver disorders with elevated serum transaminases and/or jaundice may occur; in such cases treatment should be discontinued.

There have been reports of chronic liver disease. Alteration of laboratory tests which may be minimal (transaminases elevated 1.5 to 5 times normal) or clinical signs (possible hepatomegaly) during treatment for longer than 6 months should suggest this diagnosis. Routine monitoring of liver function tests is therefore advised. Abnormal clinical and laboratory test results usually regress upon cessation of treatment, but fatal cases have been reported. Histological findings may resemble pseudo-alcoholic hepatitis, but they can be variable and include cirrhosis.
Although there have been no literature reports on the potentiation of hepatic adverse effects of alcohol, patients should be advised to moderate their alcohol intake while taking amiodarone.

Neuromuscular disorders (*see section 4.8*):
Amiodarone may induce peripheral sensorimotor neuropathy and/or myopathy. Both these conditions may be severe, although recovery usually occurs within several months after amiodarone withdrawal, but may sometimes be incomplete.

Eye disorders (*see section 4.8*)
If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed. Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness. Unless blurred or decreased vision occurs, ophthalmological examination is recommended annually.

Drug interactions (*see section 4.5*)
Concomitant use of amiodarone is not recommended with the following drugs: beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem), stimulant laxative agents which may cause hypokalaemia.

Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system (*see section 4.8.*). Because these reactions can be delayed, patients on long-term therapy should be carefully supervised. As undesirable effects are usually dose-related, the minimum effective maintenance dose should be given.

Patients should be instructed to avoid exposure to sun and to use protective measures during therapy as patients taking amiodarone can become unduly sensitive to sunlight, which may persist after several months of discontinuation of amiodarone. In most cases symptoms are limited to tingling, burning and erythema of sun-exposed skin but severe phototoxic reactions with blistering may be seen. (*see section 4.8*).

Monitoring (*see sections 4.4 and 4.8*):Before starting amiodarone, it is recommended to perform an ECG and serum potassium measurement. Monitoring of transaminases (*see section 4.4*) and ECG is recommended during treatment.

As amiodarone may induce hypothyroidism or hyperthyroidism, particularly in patients with a personal history of thyroid disorders, clinical and biological (usTSH) monitoring should be performed before starting amiodarone. This monitoring should be carried out during treatment, at six-monthly intervals, and for several months following its discontinuation. This is particularly important in the elderly. In patients whose history indicates an increased risk of thyroid dysfunction, regular assessment is recommended. Serum usTSH level should be measured when thyroid dysfunction is suspected.

Thyroid abnormalities (*see section 4.8*)
Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T_3, free-T_4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause isolated biochemical changes (increase in serum free-T_4, free-T_3 being slightly decreased or even normal) in clinically euthyroid patients. There is no reason in such cases to discontinue amiodarone treatment.

Hypothyroidism should be suspected if the following clinical signs occur: weight gain, cold intolerance, reduced activity, excessive bradycardia. The diagnosis is supported by an increase in serum usTSH and an exaggerated TSH response to TRH. T3 and T4 levels may be low. Euthyroidism is usually obtained within 3 months following the discontinuation of treatment. In life-threatening situations, amiodarone therapy can be continued, in combination with L-Thyroxine. The dose of L-Thyroxine is adjusted according to TSH levels.

Anaesthesia (see sections 4.5 and 4.8):
Before surgery, the anaesthetist should be informed that the patient is taking amiodarone.

4.5 Interaction with other medicinal products and other forms of interaction

Some of the more important drugs that interact with amiodarone include warfarin, digoxin, phenytoin and any drug which prolongs the QT interval.

Amiodarone raises the plasma concentrations of oral anticoagulants (warfarin) and phenytoin by inhibition of CYP 2C9. The dose of warfarin should be reduced accordingly. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended. Phenytoin dosage should be reduced if signs of overdosage appear, and plasma levels may be measured.

Administration of amiodarone to a patient already receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and sings associated with high digoxin levels. Clinical, ECG and biological monitoring is recommended and digoxin dosage usually has to be reduced. A synergistic effect on heart rate and atrioventricular conduction is also possible.

Combined therapy with the following drugs which prolong the QT interval in contra-indicated (see section 4.3) due to the increased risk of Torsade de Pointes; for example:

- Class Ia anti-arrhythmic drugs e.g. quinidine, procainamide, disopyramide.
- Class III anti-arrhythmic drugs e.g. sotalol, bretylium.
- Intravenous erythromycin, co-trimoxazole or pentamidine injection.
- Some anti-psychotics e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride and sertindole.
- Lithium and tricyclic anti-depressants e.g. doxepin, maprotiline, amitriptyline.
- Certain antihistamines e.g. terfenadine, astemizole, mizolastine.
- Anti-malarials e.g. quinine, mefloquine, chloroquine, halofantrine.

Combined therapy with the following drugs is not recommended:

- Beta blockers and certain calcium channel inhibitors (diltiazem, verapamil); potentiation of negative chronotropic properties and conduction slowing effects may occur.
- Stimulant laxatives which may cause hypokalaemia thus increasing the risk of torsades de pointes; other types of laxatives should be used.

Caution should be exercised over combined therapy with the following drugs which may cause hypokalaemia and/or hypomagnesaemia e.g. diuretics, systemic corticosteroids, tetracosactide, intravenous amphotericin.

In cases of hypokalaemia, corrective action should be taken and QT interval monitored. In case if Torsade de Pointes, antiarrhythmic agents should not be given; pacing may be instituted and IV magnesium may be used.

Caution is advised in patients undergoing general anaesthesia, or receiving high dose oxygen therapy. Potentially severe complications have been reported in patients taking amiodarone undergoing general anaesthesia: bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output. A few cases of adult respiratory distress syndrome most often in the period immediately after surgery have been observed. A possible interaction with a high oxygen concentration may be implicated.

<u>Flecainide</u>
Amiodarone raises plasma concentrations of flecainide by inhibition of CYP 2D6; dosage of flecainide should be adjusted.

<u>Drugs metabolised by cytochrome P450 3A4</u>
When such drugs are co-administered with amiodarone, an inhibitor of CYP 3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity.

- Ciclosporin: combination with amiodarone may increase ciclosporin plasma levels. Dosage should be adjusted.
- Fentanyl: combination with amiodarone may enhance the pharmacologic effects of fentanyl and increase the risk of its toxicity.
- Other drugs metabolised by CYP 3A4: lidocaine, tacrolimus, sildenafil, midazolam, ergotamine; simvastatin and other statins metabolised by CYP 3A4 (increased risk of muscular toxicity).

4.6 Pregnancy and lactation

Pregnancy
In view of its effect on the foetal thyroid gland, amiodarone is contraindicated during pregnancy, except in exceptional circumstances.

If, because of the long half life of amiodarone, discontinuation of the drug is considered prior to planned conception, the real risk of recurrence of life threatening arrhythmias should be weighed against the unknown possible hazard for the foetus.

Lactation
Amiodarone is excreted into the breast milk in significant quantities and breast-feeding is contraindicated.

4.7 Effects on ability to drive and use machines

According to the safety data for amiodarone, there is no evidence that amiodarone impairs the ability to drive a vehicle or operate machinery.

4.8 Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention: very common (>= 10%), common (>= 1% and < 10%); uncommon (>= 0.1% and < 1%); rare (>= 0.01% and < 0.1%), very rare (< 0.01%).

Blood and lymphatic system disorders:
- Very rare
  - Haemolytic anemia.
  - Aplastic anaemia.
  - Thrombocytopenia.

Cardiac disorders:
- Common: bradycardia, generally moderate and dose-related.
- Uncommon:
  - Onset or worsening of arrhythmia, sometimes followed by cardiac arrest (see sections 4.4 and 4.5.).
  - Conduction disturbances (sinoatrial block, AV block of various degrees) (see section 4.4).
- Very rare: marked bradycardia or sinus arrest in patients with sinus node dysfunction and / or in elderly patients.

Endocrine disorders (*see section 4.4*):
- Common:
  - Hypothyroidism.
  - Hyperthyroidism, sometimes fatal.

Eye disorders:
- Very common: corneal microdeposits usually limited to the area under the pupil, which are usually only discernable by slit-lamp examinations. They may be associated with coloured halos in dazzling light or blurred vision. Corneal micro-deposits consist of complex lipid deposits and are reversible following discontinuation of treatment. The deposits are considered essentially benign and do not require discontinuation of amiodarone.
- Very rare: optic neuropathy / neuritis that may progress to blindness (see section 4.4).

Gastrointestinal disorders:

- Very common: benign gastrointestinal disorders (nausea, vomiting, dysgeusia) usually occurring with loading dosage and resolving with dose reduction.

Hepato-biliary disorders: (*see section 4.4.*).

- Very common: isolated increase in serum transaminases, which is usually moderate (1.5 to 3 times normal range), occurring at the beginning of therapy. It may return to normal with dose reduction or even spontaneously.
- Common: acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, which are sometimes fatal
- Very rare: chronic liver disease (pseudo alcoholic hepatitis, cirrhosis), sometimes fatal.

Investigations:

- Very rare: increased in blood creatinine.

Nervous system disorders:

- Common:
  - Extrapyramidal tremor, for which regression usually occurs after reduction of dose or withdrawal.
  - Nightmares.
  - Sleep disorders.
- Uncommon: peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the drug (see section 4.4).

- Very rare:
  - Cerebellar ataxia, for which regression usually occurs after reduction of dose or withdrawal.
  - Benign intracranial hypertension (pseudo- tumor cerebri).
  - Headache.
  - Vertigo.

Reproductive system and breast disorders:

- Very rare:
  - Epididymo-orchitis.
  - Impotence.

Respiratory, thoracic and mediastinal disorders:

- Common: pulmonary toxicity [hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia (BOOP)], sometimes fatal (see section 4.4).

- Very rare:
  - Bronchospasm in patients with severe respiratory failure and especially in asthmatic patients.
  - Adult acute respiratory distress syndrome, sometimes fatal, most often immediately after surgery (possible interaction with a high oxygen concentration) (see sections 4.4. and 4.5).

Skin and subcutaneous tissue disorders:

- Very common: photosensitivity (see section 4.4),
- Common: slate grey or bluish pigmentations of light-exposed skin, particularly the face, in case of prolonged treatment with high daily dosages; such pigmentations slowly disappear following treatment discontinuation.

- Very rare:
  - Erythema during the course of radiotherapy.
  - Skin rashes, usually non- specific.
  - Exfoliative dermatitis.
  - Alopecia.

Vascular disorders:
- Very rare: vasculitis.

4.9 Overdose

Little information is available regarding acute overdosage with amiodarone. Few cases of sinus bradycardia, heart block, attacks of ventricular tachycardia, Torsades de Pointes, circulatory failure and hepatic injury have been reported.

In the event of overdose treatment should be symptomatic, gastric lavage may be employed to reduce absorption in addition to general supportive measures. The patient should be monitored and if bradycardia ensues, beta-adrenostimulants or glucagon may be given.

Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of amiodarone, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended.

Neither amiodarone or its metabolites is dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: CO1B D01.
Pharmacotherapeutic group: Antiarrhythmics, Class III.

Amiodarone slows sinoatrial, atrial and nodal conduction and increases the refractory period at the atrial, nodal and ventricular levels but does not alter intraventricular conduction. There is also slowing in conduction and prolongation of refractory periods in accessory atrioventricular pathways.

Amiodarone has anti-adrenergic (non-competitive alpha and beta blocker) effects. It inhibits the metabolic and biochemical effects of catecholamines on the heart and inhibits Na^+ and K^+ activated ATP-ase.

Amiodarone has anti-ischaemic and haemodynamic effects. It causes a moderate drop in peripheral resistance and decrease in heart rate leading to a reduction in oxygen intake. It causes an increase in coronary output due to a direct effect on the smooth muscle of the myocardial arteries. Cardiac output is maintained due to a decrease in aortic pressure and peripheral resistance.

A univariate analysis (EMIAT) suggested that all-cause mortality is reduced on amiodarone treatment in patients with an ejection fraction less than 30 %, with arrhythmia on the initial Holter, on beta-blocker treatment, and with an increased initial heart rate.

5.2 Pharmacokinetic properties

Following oral administration absorption is slow and variable with an approximate mean of 50 %, and may be prolonged due to enterohepatic cycling. Following single administration, peak plasma concentrations are reached after 3-7 hours. Therapeutic effects are usually observed after one week (from a few days to two weeks depending on the loading dose). Due to the above characteristics, loading doses should be used in order to obtain rapidly the tissue levels necessary to have a therapeutic effect.

Amiodarone has a large but variable volume of distribution because of extensive accumulation in various sites (adipose tissue, highly perfused organs such as the liver, lung and spleen). Amiodarone is highly protein bound (>95 %).

The major metabolite is desethylamiodarone. Amiodarone has a long half-life and shows considerable individual variability (from 20 to 100 days). During the first days of therapy, the drug accumulates in almost all tissues, especially the adipose tissue. Elimination occurs after a few days and steady-state plasma concentration is reached between one and several months depending upon the individual patient.

Renal excretion is minimal; excretion is mainly via the bile and the faeces.

After treatment discontinuation, the elimination continues over several months; the persistence of a pharmacodynamic effect over 10 days to one month should be taken into account.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Amiodarone Hydrochloride 200mg tablets are supplied in PVC/aluminium blister packs of 28 and 30 tablets further packed in cardboard cartons.

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

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