SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

AMIODARONE TABLETS BP 100mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

100mg of Amiodarone hydrochloride

3 PHARMACEUTICAL FORM

Tablet.

White, circular, uncoated tablet impressed “C” and the identifying letters “RD” on either side of a central division line on one face, with the reverse plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome.

Atrial flutter and fibrillation when other drugs cannot be used.

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

Tablets are used for stabilisation and long term treatment.

4.2 Posology and method of administration

Posology
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 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.
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 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. In patients with potentially lethal arrythmias the long half life is a valuable safeguard as omission of occasional doses does not significantly influence the overall therapeutic effect.
Children: The safety and efficacy of amiodarone in children has not been established.
Currently available data are described in sections 5.1 and 5.2.
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).
Method of Administration
For oral administration.

4.3 Contraindications

- Known hypersensitivity to the active ingredient or any of the excipients. The amiodarone molecule contains iodine so hypersensitivity reactions to iodine are possible (one 200mg tablets contains approximately 75mg of iodine).
- The combination of amiodarone with drugs which prolong the QT interval is contraindicated (see section 4.5) due to the increased risk of Torsades de Pointes; for example:
  - antiarrhythmic drugs *eg*: quinidine, procainamide, disopyramide.
  - beta-blockers *eg*: sotalol
  - antibacterial drugs *eg*: parentral erythromycin, moxifloxacin, co-trimoxazole or pentamidine injection
  - antipsychotics *eg*: amisulpride, sertindole, chlorpromazine, thioridazine, pimozide, haloperidol, fluphenazine
  - lithium and tricyclic antidepressants *eg*: doxepin, maprotiline, amitriptyline
  - antihistamines *eg*: terfenadine, mizolastine

– antimalarials *eg*: artemether/lumefantrine, chloroquine, mefloquine and quinine

Amiodarone should not be used in patients with the following conditions:

- sinus bradycardia and sinoatrial 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. Thyroid function tests should be performed prior to therapy in all patients
- severe hypotension
- severe respiratory failure
- women who are pregnant (except under exceptional circumstances) or breast feeding (see section 4.6).

4.4 Special warnings and precautions for use

Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system. Patients on long term treatment should be carefully supervised because these reactions may be delayed. The minimum effective maintenance dose should be given because undesirable effects are usually dose related.
The anaesthetist should be informed that the patient is taking amiodarone before surgery. (see sections 4.5 and 4.8).

- *Blood disorders*

Amiodarone should not be used in patients with porphyria. It should be prescribed only when the benefit outweighs the risk and in such cases treatment should be discussed with an expert centre.

- *Endocrine disorders*

Amiodarone may induce hypothyroidism or hyperthyroidism, particularly in patients with a personal history of thyroid disorders. Clinical and biological monitoring, including ultrasensitive TSH (usTSH) should be performed prior to therapy in all patients. Monitoring should be carried out before treatment is started and at 6 monthly intervals during treatment. 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.

Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T3, free-T4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of levothyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in free-T4, free-T3 being slightly decreased or even normal) in clinically euthyroid patients. There is no reason in such cases to discontinue amiodarone treatment if there is no clinical or further biological (usTSH) evidence of thyroid disease.

Hypothyroidism: 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 thyrotrophin releasing hormone (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 levothyroxine. The dose of levothyroxine is adjusted according to TSH levels.

Hyperthyroidism: 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 and congestive heart failure should alert the physician. The diagnosis is supported by a decrease in serum usTSH level, an elevated T3 and a reduced TSH response to TSH. Elevation of reverse T3 (rT3) may also be found. Therapy should be withdrawn in patients who develop hyperthyroidism. Clinical recovery usually occurs within a few months but severe cases, sometimes resulting in fatalities, have been reported. Clinical recovery precedes the normalisation of thyroid function tests. 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. prednisolone $1mg.kg^{-1}$) may be required for several weeks (see section 4.8).

- *Nervous system disorders*

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

- *Eye disorders*

If blurred or decreased vision occurs, complete ophthalmological 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. Routine ophthalmological examination is recommended annually (see section 4.8).

- *Cardiac disorders*

Excessive dosage of amiodarone 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. Inotropic sympathomimetics or glucagon may be given if necessary. The insertion of a pacemaker should be considered if bradycardia is severe and symptomatic because of the long half life of amiodarone.

Oral amiodarone is not contraindicated in patients with latent or manifest heart failure but caution should be exercised as, occasionally, existing heart failure may be worsened. Amiodarone may be used with other appropriate therapies in such patients. The pharmacological action of amiodarone induces QT prolongation (related to prolonged repolarisation) with the possible development of U waves and deformed T waves. These ECG changes do not reflect toxicity**.**

The heart rate may decrease markedly in elderly patients.

Treatment should be discontinued in case of onset of second or third degree AV block, sinoatrial block or bifascicular block.

Amiodarone has a weak proarrhythmic 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.

An ECG should be performed and serum potassium should be measured before starting treatment with amiodarone. ECG monitoring is recommended during treatment (see section 4.8).

Primary Graft Dysfunction post cardiac transplant
In retrospective studies, amiodarone use in the transplant recipient prior to heart transplant has been associated with an increased risk of primary graft dysfunction (PGD). PGD is a life-threatening complication of heart transplantation that presents as left, right or biventricular dysfunction occurring within the first 24 hours of transplant surgery for which there is no identifiable secondary cause (see section 4.8). Severe PGD may be irreversible. For patients who are on the heart transplant waiting list, consideration should be given to use an alternative antiarrhythmic drug as early as possible before transplant.

- *Respiratory, thoracic and mediastinal 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 pneumonia). 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 it 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 rays 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. However, initial radiological changes may be difficult to distinguish from pulmonary venous congestion and high-definition computerised tomography scans may therefore be more useful than chest x-rays in confirming a diagnosis. 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.

- *Hepato-biliary disorders*

Amiodarone is associated with a variety of hepatic effects, including cirrhosis, hepatitis, jaundice and hepatic failure. Some fatalities have been reported, usually following long term therapy. It is advisable to monitor liver function, particularly transaminases, before treatment and every 6 months thereafter.

At the beginning of therapy, elevation of serum transaminases (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 (see section 4.8).

- *Skin and subcutaneous tissue disorders*

Patients taking amiodarone can become unduly sensitive to sunlight and they should be instructed to avoid exposure to sun and to use protective measures during therapy. Sun sensitivity may persist for several months after discontinuing 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).

- *Interactions with other drugs*

Concomitant use of amiodarone is not recommended with the following drugs (see section 4.5):

- drugs that cause hypokalaemia
- inhibitors or inducers of cytochrome P450 3A4
- calcium channel blockers such as verapamil and diltiazem
- flecainide
- sofosbuvir*.

*Life-threatening cases of bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone. Bradycardia has generally occurred within hours to days, but later cases have been mostly observed up to 2 weeks after initiating HCV treatment.
Amiodarone should only be used in patients on sofosbuvir- containing regimen when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated. Should concomitant use of amiodarone be considered necessary, it is recommended that patients undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.
Due to the long half-life of amiodarone, cardiac monitoring as outlined above should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofosbuvir- containing regimen.
All patients receiving amiodarone in combination with sofosbuvir-containing regimen should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

- Combined therapy with the following drugs which prolong the QT interval is contra-indicated (see section 4.3) due to the increased risk of Torsades de Pointes; for example:
  - antiarrhythmic drugs *e.g.*: quinidine, procainamide, disopyramide
  - beta-blockers *e.g.*: sotalol
  - antibacterial drugs *e.g.*: parentral erythromycin, moxifloxacin, co-trimoxazole or pentamidine injection
  - antipsychotics *e.g.*: amisulpride, sertindole, chlorpromazine, thioridazine, pimozide, haloperidol, fluphenazine
  - lithium and tricyclic antidepressants *e.g.*: doxepin, maprotiline, amitriptyline
  - antihistamines *e.g.*: terfenadine, mizolastine
  - antimalarials *e.g.*: artemether/lumefantrine, chloroquine, mefloquine and quinine.

- The following combinations are not recommended:
  - Calcium channel blockers - co-administration of diltiazem or verapamil with amiodarone has an additive effect in depressing both sinus and AV node function and concurrent use is not recommended, particularly in patients whose cardiac function is already compromised.
  - Stimulant laxatives - may cause hypokalaemia thus increasing the risk of torsades de pointes (see section 4.4).
  - Caution should be exercised over combined therapy with the following drugs which may also 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 of torsades de pointes antiarrhythmic agents should not be given, pacing may be instituted and IV magnesium may be used.
  - Anaesthetics, general - potentially severe complications may occur in patients undergoing general anaesthesia**,** including bradycardia unresponsive to atropine, hypotension, conduction disturbances and decreased cardiac output**.** Special care is required in patients undergoing coronary bypass surgery. Amiodarone may persist long after therapy has been withdrawn and the anaesthetist should be aware of patients who are taking amiodarone or have discontinued it within a few weeks before surgery (see section 4.4).
  - Anaesthetics, local - the risk of myocardial depression is increased when amiodarone is co-administered with bupivacaine or levobupivacaine because of additive effects on the myocardium.
  - High dose oxygen therapy – 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.
  - Anticoagulants - amiodarone inhibits the hepatic metabolism of coumarins, such as warfarin, resulting in enhanced anticoagulant activity and bleeding may occur if the anticoagulant dose is not reduced. The onset of the interaction may be up to 2 weeks and it may persist long after amiodarone has been withdrawn. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended.
  - Antiepileptics - amiodarone may inhibit the hepatic metabolism of phenytoin resulting in an increase in plasma levels. The dose of phenytoin may need to be reduced in patients taking amiodarone. Amiodarone plasma levels may be reduced by co-administration with phenytoin.
  - Antimigraine - amiodarone may lead to increased plasma levels of ergometrine, which may possibly lead to an increase in ergometrine toxicity.
  - Cardiac glycosides – administration of amiodarone to a patient already receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels. Clinical, ECG

and biological monitoring is recommended and digoxin dosage should be halved. A synergistic effect on heart rate and atrioventricular conduction is also possible.
- Flecainide - amiodarone inhibits the hepatic metabolism and elimination of flecainide. The augmentation of the electrophysiological effects on conduction may also be disproportionate when amiodarone and flecainide are administered concurrently. The dose of flecainide should be reduced by about 50% but patients should be monitored carefully because of interindividual variation in response. The interaction can take 2 weeks to develop and may persist for several weeks after amiodarone is withdrawn due to its slow clearance from the body.
- Lipid regulating drugs - the risk of myopathy/rhabdomyolysis is increased in patients taking simvastatin and amiodarone concomitantly. Doses of simvastatin in excess of 20mg should be avoided.
- Orlistat – plasma levels of amiodarone may be decreased by concomitant administration with orlistat.
- Sofosbuvir-containing regimens- coadministration of amiodarone may lead to serious symptomatic bradycardia. If coadministration cannot be avoided, cardiac monitoring is recommended (see section 4.4).

- Cytochrome P450 interactions :
  - Substances that inhibit CYP 3A4 may decrease the metabolism and increase serum concentrations of amiodarone, with the potential for toxicity. Examples include erythromycin, azole antifungals and protease inhibitors. Grapefruit juice should also be avoided.
  - Conversely, substances that induce CYP 3A4 may decrease serum concentrations of amiodarone with the potential for loss of efficacy. Examples include carbamazepine, phenytoin, rifampicin, midazolam, lidocaine, fentanyl, sildenafil and St John's Wort
  - Plasma levels of ciclosporin, tacrolimus and sirolimus may be increased by the concomitant administration of amiodarone. A reduction in the dose of Ciclosporin may be necessary to maintain the plasma concentration within the therapeutic range.

If combination therapy cannot be avoided then appropriate monitoring should be considered.

4.6 Pregnancy and lactation

Pregnancy

Although no teratogenic effects have been observed in animals, there are insufficient data on the use of amiodarone during pregnancy in humans to judge any possible toxicity.

As amiodarone crosses the placenta its use is generally contraindicated except in women with exceptional circumstances. Serious foetal abnormalities such as congenital goitre, hypothyroidism or hyperthyroidism have been reported and are directly attributed to the administration of amiodarone.

Amiodarone has a very long elimination half life and discontinuation should be considered several months before conception to avoid exposure in early gestation.

Due to the large proportion of iodine in amiodarone newborns exposed to amiodarone should have thyroid function tests performed.

Lactation

Amiodarone is present breast milk in significant quantities and the effects of exposure are unknown, therefore amiodarone is contraindicated in breast feeding.

In addition, due to the long half life and prolonged exposure hypothyroidism may occur in the infant.

4.7 Effects on ability to drive and use machines

As amiodarone can cause vertigo or visual disturbances patients should make sure they are not affected before they drive or operate machinery.

4.8 Undesirable effects

Amiodarone can cause serious adverse reactions affecting the lung, liver, thyroid gland, skin and peripheral nervous system (see below). Because these reactions can be delayed, patients on long term treatment should be carefully supervised.

Adverse reactions are classified by system organ class and ranked under headings 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%), unknown (frequency cannot be estimated from the available data).

- *Blood and lymphatic system disorders*

Very rare: Haemolytic anaemia, aplastic anaemia, thrombocytopenia.
In patients taking amiodarone there have been incidental findings of bone marrow granulomas. The clinical significance of this is unknown.
Unknown: Neutropenia, agranulocytosis.

- *Immune system disorders*

Very rare: Hypersensitivity reaction involving vasculitis, renal involvement with moderate elevation of creatinine levels or thrombocytopenia.
Unknown: Anaphylactic reaction, anaphylactic shock.

- *Endocrine disorders*

Common: Hypothyroidism, hyperthyroidism (sometimes fatal) (see section 4.4).
Rarely: Refractory thyrotoxicosis (usually sudden, severe and short lived).
Very Rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

- *Nervous system disorders*

Common: Extrapyramidal tremor (regression usually occurs after reduction of dose or withdrawal)**,** nightmares, sleep disorders.
Uncommon: Peripheral sensorimotor neuropathy and/or myopathy (usually reversible on withdrawal of amiodarone) (see section 4.4).
Very rare: Cerebellar ataxia (regression usually occurs after reduction of dose or withdrawal), benign intracranial hypertension, headache, vertigo.
Unknown: Parkinsonism, parosmia

- *Eye disorders*

Very common: Corneal microdeposits, usually limited to the area under the pupil, which are usually only discernible by slit lamp examination. They may be associated with coloured halos in dazzling light or blurred vision. Corneal microdeposits are lipid complexes 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).

- *Cardiac disorders*

*Common**:*** Bradycardia, generally moderate and dose related.
Uncommon: Onset or worsening of arrhythmia (including Torsade de pointes), sometimes followed by cardiac arrest, conduction disturbances (sinoatrial block, AV block of varying degrees) (see sections 4.4 and 4.5).
Very rare: Marked bradycardia or sinus arrest in patients with sinus node dysfunction and/or in elderly patients.

- *Respiratory, thoracic and mediastinal disorders*

Common: Pulmonary toxicity (hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia), sometimes fatal (see section 4.4).
Very rare: Bronchospasm in patients with severe respiratory failure and especially in asthmatic patients, adult respiratory distress syndrome following surgery (possible interaction with a high oxygen concentration). (see section 4.5).

- *Gastrointestinal disorders*

Very common: Benign gastrointestinal disorders (nausea, vomiting, dysgeusia, metallic taste)**,** usually occurring with loading dosage and resolving with dose reduction.
Common: Constipation
Uncommon: Dry mouth
Unknown: Pancreatitis (acute)

- *Hepato-biliary disorders*

Very common: Isolated increase in serum transaminases which is usually moderate (1.5 to 3 times normal range) and occurs at the beginning of therapy. It may return to normal with dose reduction or even spontaneously (see section 4.4).
Common: Acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, which are sometimes fatal (see section 4.4).
Very rare: Chronic liver disease (pseudo-alcoholic hepatitis, cirrhosis), sometimes fatal (see section 4.4).

- *Skin and subcutaneous tissue disorders*

Very common: Photosensitivity (see section 4.4).
*Common**:*** Slate grey or bluish pigmentation of light exposed skin, particularly the face, in patients undergoing prolonged treatment at high daily dosages; such pigmentation slowly disappears following treatment discontinuation, eczema.
*Very rare**:*** Erythema during the course of radiotherapy, skin rashes (usually non-specific)**,** exfoliative dermatitis, alopecia**.**
Unknown: severe skin reactions as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), bullous dermatitis, Drug reaction with eosinophilia and systematic symptoms (DRESS).

- *Reproductive system and breast disorders*

Very rare: Epididymo-orchitis, impotence.

- *Metabolic and nutrition disorders*

Unknown: Decreased appetite

- *Psychiatric disorders:*

Common: Libido decreased
Unknown: Delirium (including confusion), hallucination.

- *Injury, poisoning and procedural complications:*

Not known: Primary graft dysfunction post cardiac transplant (see section 4.4).

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; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The fatal dose of amiodarone is not known. Ingestion of 8g has caused no symptoms and patients have survived overdoses of 15g. However, some patients may develop cardiac features at lower doses.

Symptoms

Nausea, vomiting, sweating, hypotension, tachycardia and bradycardia may occur. There may also be ECG changes including prolongation of the QT interval, ventricular tachycardia, atrial flutter, premature beats, Torsades de Pointes and AV block.

Treatment

No specific antidote to amiodarone overdose is known. Treatment is largely symptomatic and supportive and may need to be prolonged because of the long half life of amiodarone. Haemodialysis has no value in eliminating amiodarone. Activated charcoal 50g may be used if an adult presents within 1 hour of ingestion of 2g or 10 to 15g for a child ingesting $20mg.kg^{-1}$ within 1 hour. Gastric lavage may be considered in adults within 1 hour of a potentially life threatening overdose. ECG and electrolytes should be monitored for at least 24 hours after the overdose. Torsades de Pointes may be treated with magnesium sulfate 8 to 10mmol (4 to 5ml of $2mmol.ml^{-1}$ solution) intravenously over 30 to 120 seconds, repeated twice at intervals of 5 to 15 minutes if necessary. Alternatively, or if these measures fail, Torsades de Pointes may be abolished by increasing the underlying heart rate. This can be achieved by atrial or ventricular pacing or by isoprenaline infusion to achieve a heart rate of 90 to 110 beats per minute.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C01B D01

Amiodarone hydrochloride is a class III antiarrhythmic.

No controlled paediatric studies have been undertaken.

In published studies the safety of amiodarone was evaluated in 1118 paediatric patients with various arrhythmias. The following doses were used in paediatric clinical trials.

Oral

- Loading dose: 10 to 20 mg/kg/day for 7 to 10 days (or 500 mg/m^2 /day if expressed per square meter)
- Maintenance dose: the minimum effective dosage should be used; according to individual response, it may range between 5 to 10 mg/kg/day (or 250 mg/m^2/day if expressed per square meter)

Intravenous

- Loading dose: 5 mg/kg body weight over 20 minutes to 2 hours,
- Maintenance dose: 10 to 15 mg/kg/day from few hours to several days

If needed oral therapy may be initiated concomitantly at the usual loading dose.

5.2 Pharmacokinetic properties

Amiodarone is strongly protein bound and the plasma half life is usually of the order of 50 days. However there may be considerable inter-patient variation; in individual patients a half life of less than 20 days and a half life of more than 100 days has been reported. High doses of amiodarone, for example 600mg/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half life of the drug, a maintenance dose of only 200mg/day, or less is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by amiodarone.

No controlled paediatric studies have been undertaken. In the limited published data available in paediatric patients, there were no differences noted compared to adults.

5.3 Preclinical safety data

In a 2-years carcinogenicity study in rats, amiodarone caused an increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinical relevant exposures. Since mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is proposed for this type of tumour induction. In the mouse, carcinomas were not observed, but a dose-dependent thyroid follicular hyperplasia was seen. These effects on the thyroid in rats and mice are most likely due to effects of amiodarone on the synthesis and/or release of thyroid gland hormones. The relevance of these findings to man is low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Also contains: maize starch, lactose monohydrate, povidone, magnesium stearate, colloidal anhydrous silica and pregelatinised starch.

6.2 Incompatibilities

None stated.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original packaging.

6.5 Nature and contents of container

Amiodarone Tablets are supplied in blisters consisting of a 250µm thick PVC film sealed o a 25µm thick cold-hammered aluminium foil, printed with the regulatory labelling requirements.

Each box is accompanied by a patient information leaflet.

Pack sizes: 28’s, 30’s, 56’s, 60’s, 84’s, 90’s

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
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EX32 8NS

8 MARKETING AUTHORISATION NUMBER

PL 00142/0489

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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