CHEMMART AMIODARONE TABLETS

NAME OF THE MEDICINE
Amiodarone hydrochloride.

Chemical Name: 2-butyl-3-benzofuranyl 4-(2-diethylaminoethoxy)-3,5-di-iodophenyl ketone hydrochloride.

Structural Formula:

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\begin{array}{c}
\text{O} \\
\text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_3 \\
\text{O} \\
\text{C} \\
\text{I} \\
\text{I} \\
\text{OCH}_2 \text{CH}_2 \text{N(C}_2\text{H}_5)_2 \\
\end{array}
\]

*HCl

Molecular Formula: C\text{_{25}}H\text{_{29}}N\text{_{12}}O\text{_{3}}.HCl
Molecular Weight: 681.8
CAS Registry Number: 19774-82-4

DESCRIPTION
Amiodarone hydrochloride is a white or almost white, fine crystalline powder, very slightly soluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in alcohol and very slightly soluble in hexane.

PHARMACOLOGY
Pharmacokinetics
In general, pharmacokinetic data relating to amiodarone are incomplete. Amiodarone is incompletely and erratically absorbed following oral administration. Absolute bioavailability ranges from 22 to 86% but there is extensive intersubject variation. First-pass metabolism in the gut wall and/or in the liver may be a factor in determining the availability of the drug.

Food increases the rate and extent of absorption of amiodarone, amiodarone should be administered consistently with regard to meals.

A high pressure liquid chromatography (HPLC) method is available for estimation of amiodarone plasma levels. However, the value of this is limited because the correlation of therapeutic effect and plasma level has not been established. Steady state plasma levels are generally around 1 to 2 microgram/mL, although intersubject variations are common.
Considerably higher values have been reported, especially subsequent to large single doses. Peak plasma concentrations of 6.9 ± 4.2 microgram/mL have been recorded following a single dose of 1600 mg and 1.7 ± 0.3 microgram/mL after a single dose of 800 mg. Steady state levels of 1.57 ± 0.1 microgram/mL and 3.9 microgram/mL have been recorded after daily oral dosing in the range 800 to 1800 mg.

The half-life of amiodarone is long and with chronic oral dosing can be from 14 to 110 days, but is usually in the range of 14 to 59 days. The principal metabolite of amiodarone, which has been detected in the plasma and other tissues, is desethylamiodarone. This metabolite is reported to have a longer half-life than amiodarone, i.e. ten hours after a single dose of amiodarone and 60 to 90 days after chronic dosing with amiodarone. The activity of this metabolite is not known. Amiodarone is highly protein bound and is thought to bind strongly to protein at concentrations of 10 microgram/mL. It is believed that most of the drug is excreted via the liver and gastrointestinal tract by biliary excretion. There may be some hepatic recirculation.

The apparent volume of distribution after oral amiodarone 200 to 400 mg is 6.31 ± 4.93 L/kg. Amiodarone appears to accumulate in adipose tissue and in highly perfused organs (lung, bone marrow, adrenals, liver, pancreas, heart, spleen and kidney). Concentration of amiodarone in packed red blood cells is approximately 60% of that in plasma.

Pharmacodynamics

Site and Mode of Action

Amiodarone is a Class III antiarrhythmic agent prolonging the action potential duration and hence refractory period of atrial, nodal and ventricular tissues, thereby giving a very broad spectrum of activity. An increase in the refractory period of the atrial cells is a major contributing action to the control of atrial tachyarrhythmias.

A reduction in the permeability of the atrioventricular node, both anterograde and retrograde, explains the efficacy of the drug in nodal tachycardias caused by re-entry through the atrioventricular node.

Its action on ventricular arrhythmias is explained by a number of mechanisms. The effect on the atrium and atrioventricular node results in a reduction in the frequency of stimuli reaching the ventricle, thus giving the ventricular cell mass time to repolarise in cases where there has been desynchronisation of the refractory periods. Furthermore, lengthening of the refractory period of the His-Purkinje system and ventricular contractile fibres reduces or prevents micro re-entry.

Amiodarone increases coronary blood flow, decreases cardiac oxygen requirements without producing negative inotropic effects and also suppresses ectopic pacemakers, and this is particularly valuable in arrhythmias associated with ischaemic damage or angina pectoris.

The site and mode of action of amiodarone can be summarised in terms of its effect on myocardial electrophysiology.

Myocardial Electrophysiology

Sinus Node
It decreases sinus automaticity by reducing the slow diastolic depolarisation gradient in the nodal cell. This is a direct effect and is not mediated through the sympathetic or parasympathetic system.

Atrioventricular Node
It reduces the speed of conduction and increases the refractory period of the atrioventricular node.

His-Purkinje System
It increases the refractory period but does not modify the speed of conduction of the His-Purkinje system.

Contractile Fibres
It increases the action potential but does not alter the rate of depolarisation of the atrial or ventricular myocardial cells; an effect that is more marked in the atria than the ventricles.
INDICATIONS
Severe cases of tachyarrhythmias (e.g. Wolff-Parkinson-White syndrome; supraventricular, nodal and ventricular tachycardias; atrial flutter and fibrillation; ventricular fibrillation) not responding to other therapy. Treatment should be initiated in hospital. It is recommended that the patient should be regularly monitored for possible toxicity (e.g. thyroid function, chest X-ray, ophthalmological examination, hepatic function) during the entire course of therapy and for several months after discontinuation.

CONTRAINDICATIONS
- Pregnancy and lactation (see PRECAUTIONS, Use in Pregnancy, and Use in Lactation).
- In patients in whom bradycardia or atrioventricular block is sufficient to cause syncope, patients with sick sinus syndrome (risk of sinus arrest) or with severe conduction disorders, amiodarone should only be used in conjunction with a pacemaker.
- Evidence or a history of thyroid dysfunction.
- Known hypersensitivity to amiodarone or iodine or to any of the excipients.
- Combined therapy with drugs that may induce Torsades de Pointes (see PRECAUTIONS-Interactions with other Medicines).
- Hypotension, severe respiratory failure, myocardiopathy, heart failure, circulatory collapse, and severe arterial hypotension.
- Sinus bradycardia and sinoatrial heart block.

PRECAUTIONS
It is recommended to perform an ECG and serum potassium measurement before treatment initiation.

As amiodarone may induce thyroid disorders (see ADVERSE EFFECTS), particularly in patients with personal or family history of thyroid disorders, clinical and biological monitoring is recommended before starting treatment, ultrasensitive TSH (usTSH) assay, during treatment and for several months following treatment discontinuation. Serum usTSH levels should be measured when thyroid dysfunction is suspected.

Regular monitoring of liver function tests (transaminases) is recommended during treatment.

Anaesthesia: Before surgery the anaesthetist should be informed that the patient is taking amiodarone.

Pacemakers/Implantable Defibrillators
In the context of chronic administration of antiarrhythmic drugs, cases of increase in ventricular defibrillation and/or pacing threshold of pacemakers or implantable cardioverter defibrillator devices have been reported, potentially affecting their efficacy. Therefore, a repeated verification of the functioning of such devices before and during amiodarone treatment is recommended.

Use with Caution in the Following Circumstances
Heart Failure
Amiodarone is not contraindicated in patients with latent or manifest heart failure, but caution should be exercised as existing heart failure may occasionally be worsened. In such cases amiodarone should be associated with the usual cardiotonic and diuretic treatment.

Excessive doses may lead to atropine resistant bradycardia and to conduction disturbances, particularly in elderly patients or during digitalis therapy. Amiodarone, like quinidine and disopyramide, has caused atypical ventricular tachycardia (see ADVERSE EFFECTS, Cardiovascular). In patients with previous history of the above condition, amiodarone should be avoided. Use of higher doses of amiodarone is not advisable in persons with a history of atypical ventricular tachycardia previously induced by another antiarrhythmic agent.

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

Regular ECG monitoring is recommended in patients on long-term therapy with amiodarone. U waves, deformed T waves and QT prolongation may occur in the ECG because of the fixing of amiodarone in the myocardial tissues, and is not an indication for withdrawing amiodarone. The prolongation of QT interval occurs in almost all patients, as this is related to the electrophysiological and antiarrhythmic properties of the drug. Prolongation of the actual QT above 0.6 seconds rather than QTc or QRS widening, may be an important warning sign that requires modification of therapy. Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm (atypical ventricular tachycardia; Torsades de Pointes), particularly in elderly patients or during digitalis or other antiarrhythmic therapy. In such circumstances amiodarone should be temporarily withdrawn.

**Ocular Changes**

Corneal deposits develop in almost all patients (see ADVERSE EFFECTS, Ocular) and regular ophthalmological monitoring (e.g. slit lamp biomicroscopy, visual acuity, ophthalmoscopy) is recommended. If blurred or decreased vision occurs, 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.

**Pulmonary Lesions**

Clinical and radiological evidence of pulmonary fibrosis and/or pneumonitis has been reported, sometimes presenting as unexplained or disproportionate dyspnoea (see ADVERSE EFFECTS, Respiratory). Regular chest X-ray should be performed routinely in patients undergoing long-term therapy. The effect has usually been reversible with corticosteroid therapy and/or reduction or withdrawal of amiodarone therapy.

Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity (see ADVERSE EFFECTS).

**Impaired Hepatic Function**

Elevation of hepatic enzyme levels (e.g. serum aspartate aminotransferase, serum alanine aminotransferase, glutamyl transpeptidase) occurs quite commonly in patients undergoing treatment with amiodarone and in some cases are asymptomatic. The changes appear to be dose dependent rather than an idiosyncratic type. Hepatotoxicity has occasionally been reported (see ADVERSE EFFECTS, Hepatic) and close monitoring of hepatic function is recommended as soon as amiodarone is started and regularly during treatment. If patients present with abnormal liver function tests, dosage reduction should be considered. If liver function tests continue to rise despite reduction in dosage or in situations where dosage reduction is not feasible, discontinuation of the drug should be considered. Acute liver disorders (including severe hepatocellular insufficiency or hepatic failure, sometimes fatal) and chronic liver disorders may occur with oral and intravenous forms. Therefore, amiodarone dose should be reduced or the treatment discontinued if the transaminases increase exceeds three times the normal range. Clinical and biological signs of chronic liver disorders due to oral amiodarone may be minimal and reversible after treatment withdrawal, however fatal cases have been reported.

Because of the potential risk of hepatotoxicity and/or accumulation, amiodarone should be used with extreme caution in patients with hepatic disease.

**Skin Reactions**

Photosensitivity is quite common (see ADVERSE EFFECTS, Dermatological) and there is a wide spectrum of skin reactions, ranging from an increased propensity to suntan during the summer months to intense burning and erythema and swelling of the exposed area. The intensity of these reactions could be alleviated by a reduction in dosage or by application of a protective sunscreen. Patients should be instructed to avoid exposure to the sun or use protective measures during therapy.
Some patients have developed skin pigmentation (slate grey/purple colour) of the exposed areas. This pigmentation can be avoided if doses are kept as low as possible. If the pigmentation is cosmetically unsightly, amiodarone should be discontinued if alternative therapy is possible.

**Neurological Toxicity**

Peripheral neuropathy could occur in patients on long-term high dosage (generally over 400 mg/day) regimen (see **ADVERSE EFFECTS**, Nervous System). Intracellular inclusion bodies, similar to those seen in skin, have been demonstrated in peripheral nerve fibres. Sensorimotor neuropathy, with a glove and stocking distribution, and myopathy have been reported in patients. Histologically, segmental demyelination of the nerve fibres has also been demonstrated. After discontinuation of the drug, the neurological complication is slowly and incompletely resolved.

**Impaired Renal Function**

Renal excretion of the drug is minimal. This suggests that modification of the dose of amiodarone in patients with renal failure is unnecessary.

**Use in Pregnancy (Category C)**

Because of the long half-life of amiodarone and its major metabolite, and the potential to cause abnormal thyroid function and bradycardia in the fetus, its use is probably best avoided in the three months before and throughout the duration of pregnancy. Where exposure of the fetus is unavoidable, thyroid function (including thyroid stimulating hormone levels) should be assessed promptly in the newborn infant.

No teratogenic effects have been observed in animals. The drug does cross the placenta. In one study, in a 35 year old woman administered amiodarone in the last weeks of pregnancy, the transplacental passage of amiodarone and desethylamiodarone was found to be 10% and 25% respectively. Changes in maternal thyroid function were similar to those seen in other patients receiving amiodarone therapy (see **ADVERSE EFFECTS**, Endocrine) but there was no evidence of clinical hyperthyroidism. The baby's TSH level on day 4 was normal and it had no goitre and was clinically euthyroid. However, the authors caution the use of amiodarone in pregnancy or in those likely to conceive whilst on amiodarone therapy. The long half-life of the drug requires that the drug be stopped several months before conception. The possible adverse effects of amiodarone on the fetal thyroid are of concern since administration of iodine (of which there is 75 mg in a 200 mg dose of amiodarone) during pregnancy may cause fetal goitre, hypothyroidism and mental retardation.

Another patient received amiodarone 800 mg for one week (maintenance dose thereafter was 400 mg daily) in her thirty-fourth week of pregnancy. Neonatal levels of amiodarone were 25% of the maternal level. Although the infant's liver and thyroid function tests were normal, it was bradycardic during labour and for the first 48 hours after birth.

Amiodarone is contraindicated in pregnancy.

Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations.

**Use in Lactation**

As amiodarone and its desethyl metabolite are secreted in breast milk and its safety in the newborn infant has not been established, it should not be given to breastfeeding mothers. If a situation demands that amiodarone be given to a breastfeeding mother, alternative infant feeding should be instituted.

**Use in Children**

The safety and effectiveness of amiodarone has not been established. Therefore its use in children is not recommended.

**Use in the Elderly**

See “**DOSAGE AND ADMINISTRATION**”
Carcinogenicity, Mutagenesis
In a carcinogenicity study in rats, amiodarone caused a dose related increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes. Although 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 dose dependent thyroid follicular hyperplasia was seen. The relevance of these findings to humans is unknown. Clinical experience has indicated that amiodarone can effect thyroid function.

Interactions with Other Medicines

Combined Therapy Contraindicated
Combined therapy with drugs that may induce Torsade de Pointes is contraindicated (see CONTRAINDICATIONS).

Antiarrhythmic Agents: Class 1A Antiarrhythmic Agents
These include the following:

Disopyramide
Combined treatment of amiodarone and disopyramide causes an increase in the QT interval.

Procaainamide
Serum levels of procaainamide increased significantly with co-administration of amiodarone and secondary to this increase cardiac, gastrointestinal and neural toxicity developed.

Quinidine
Atypical ventricular tachycardia with QT prolongation developed after amiodarone was added to a stable quinidine regimen. This is thought to be due to either a change in the protein or receptor binding of quinidine. Serum levels of quinidine increased significantly with concomitant amiodarone therapy. Careful monitoring of the electrocardiogram for QT interval prolongation and of serum levels of quinidine is indicated when amiodarone is added to quinidine treatment.

Mexiletine
Co-administration with amiodarone increases QT interval.

Sotalol

Non-Antiarrhythmic Agents

Some neuroleptic agents
There is an increased risk of potentially lethal Torsades de Pointes.

Erythromycin IV
There is an increased risk of potentially lethal Torsades de Pointes.

Pentamidine IV
There is an increased risk of potentially lethal Torsades de Pointes.
Combined Therapy Not Recommended

Combined therapy with the following drugs is not recommended:

*Beta-Adrenergic Blocking Drugs*  
Amiodarone itself exhibits noncompetitive alpha- and beta-adrenergic inhibition. It should be used with caution in patients on beta-blockers as it may potentiate bradycardia.

*Calcium Antagonists*  
Co-administration of amiodarone with drugs of the calcium antagonist type may lead to undue bradycardia.

*Monoamine Oxidase (MAO) Inhibitors*  
Co-administration with MAOIs is contraindicated on theoretical grounds.

*Stimulant Laxative Agents*  
Their use may cause hypokalaemia and therefore increase the risk of Torsades de Pointes; other types of laxative agents should be used.

*Fluoroquinolones*  
Should be avoided in patients receiving amiodarone.

Caution to be Exercised

Caution should be exercised when using the following drugs in combination with Amiodarone:

*Agents which may induce Hypokalaemia*  
For example, diuretics inducing hypokalaemia, either alone or combined; systemic corticosteroids (gluco-, mineralo-); tetracosactide; amphotericin. It is necessary to prevent the onset of hypokalaemia (and to correct hypokalaemia); the QT interval should be monitored and, in case of ‘torsades de pointes’, antiarrhythmic agents should not be given (ventricular pacing should be initiated; IV magnesium may be used).

*Cyclosporin*  
Because of the possible increase of cyclosporin plasma levels related to a decrease of the clearance of this drug, dosages should be adjusted.

*Digoxin*  
Co-administration to patients already receiving digitalis increases plasma digoxin concentrations by about 70% and therefore precipitates toxicity and could lead to severe bradycardia and conduction disturbances with the appearance of idioventricular rhythm. The mechanism of action is unknown, but amiodarone may displace tissue glycoside or interfere with digoxin excretion. ECG and digoxin plasma levels should be monitored and patients should be observed for clinical signs of digoxin toxicity. It may be necessary to adjust dosage of digoxin treatment.

*Flecainide*  
Possible increase of flecainide plasma levels: dosage of flecainide should be adjusted.
Anaesthesia, Oxygen Therapy

Potentially severe complications have been reported in patients undergoing general anaesthesia, such as bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output.

A few cases of severe respiratory complications, such as adult acute respiratory distress syndrome, resulting sometimes in fatalities, have been observed most often in the period immediately after surgery. A possible interaction with a high oxygen concentration may be implicated.

Phenytoin

Possible increase in plasma phenytoin levels with signs of overdosage (particularly neurological signs); clinical monitoring should be undertaken and phenytoin dosage should be reduced as soon as overdosage signs appear; phenytoin plasma levels should be determined.

Warfarin & other Anticoagulant Agents

Amiodarone potentiates anticoagulant therapy and increases the risk of bleeding. More frequent monitoring of prothrombin level and dosage adjustment of oral anticoagulant during treatment with, and after discontinuation of, amiodarone therapy is necessary.

Drugs metabolised by cytochrome P450 3A4

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:

- Cyclosporin: because of the possible increase of cyclosporin plasma levels related to a decrease of the clearance of this drug, dosage should be adjusted.
- Fentanyl: combination with amiodarone may enhance the pharmacologic effects of fentanyl and increase the risk of its toxicity.
- Simvastatin and other statins metabolised by CYP 3A4: increased risk of muscular toxicity.
- Other: lignocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine.

Other

Consideration should be given to the possibility that amiodarone may alter the plasma concentration of other drugs, particularly those which are highly protein bound.

Effect on Laboratory tests

Thyroid Function Tests

Amiodarone contains two atoms of iodine and bears a structural resemblance to the molecule of thyroxine. A 300 mg maintenance dose of amiodarone has been reported to yield 9 mg/day of iodine at steady state, well in excess of the highest normal dietary intake.

As a consequence of taking the drug and in the absence of any clinical thyroid dysfunction, changes in tests of thyroid function may occur, variable in number and degree. Typically, the protein bound iodine (PBI), iodine uptake, serum thyroxine (T₄), reverse triiodothyronine (rT₃) and free thyroxine index (FTI) rise and serum triiodothyronine (T₃) falls. Abnormalities, either multiple or single, may occur in approximately 12% of patients. In particular, a low T₃ syndrome has been described, as with other drugs such as dexamethasone.
ADVERSE EFFECTS

Amiodarone has been reported to cause frequent and potentially serious toxicity. The incidence, variety and severity of the effects varies from study to study. Most of the adverse effects are also related to dosage and duration of amiodarone, concurrent use of other antiarrhythmic agents, severity of the underlying disease state, and individual variation in the pharmacokinetic profile of the drug.

More Common Reactions

Biochemical Abnormalities

Abnormal liver function tests (increased AST, ALT and alkaline phosphatase) have been reported. Abnormal thyroid function tests (see INTERACTIONS WITH OTHER MEDICINES, Laboratory Tests).

Cardiovascular

Atypical ventricular tachycardia (Torsades de Pointes). Amiodarone induced atypical ventricular tachycardia has been described. Earlier reports describe combination therapy in which other drugs, or clinical situations, could have been implicated. However, in two patients given disopyramide and amiodarone, on withdrawal of the amiodarone, the disopyramide did not induce atypical ventricular tachycardia.

Bradycardia: Significant sinus bradycardia has occasionally been reported.

Cardiac failure: Exacerbation of cardiac failure has been reported rarely.

Other: Sinus arrest and intrahisian block have been reported.

Dermatological

Photosensitivity commonly occurs in patients on amiodarone therapy. This can usually be alleviated by the use of topical sunscreens and other protective measures. Less frequently, bluish skin discolouration and slate grey facial pigmentation have been reported. These adverse effects are partially dependent on dose and duration of treatment. Erythema, facial flushing and hair loss have been reported.

Skin rashes, usually non-specific, including exceptional cases of exfoliative dermatitis have been reported; the relationship with the drug has not been formally established.

Gastrointestinal

Nausea and more rarely vomiting, anorexia, constipation and dysgeusia have been reported.

Endocrine

Effects on the Thyroid:

Both hyperthyroidism and hypothyroidism have occurred during or soon after treatment with amiodarone. Simple monitoring of the usual biochemical tests is confusing because some (protein bound iodine (PBI) and $^{131}$I uptake) are invalidated and others ($T_4$, $T_3$ and free thyroxine index (FTI)) may be altered where the patient is clearly euthyroid. Clinical monitoring is therefore recommended before starting treatment, during treatment and should be continued for some months after discontinuation of amiodarone treatment. Serum usTSH level should be measured when thyroid dysfunction is suspected.

The signs of thyroid hyperactivity to be sought are weight loss, asthenia, restlessness, a recurrence of cardiac dysrhythmia, onset of angina or congestive heart failure. The diagnosis may be confirmed by the finding of an elevated serum triiodothyronine ($T_3$), a low level of thyroid stimulating hormone (TSH) and a reduced TSH response to thyrotropin releasing hormone (TRH). (Elevation of reverse triiodothyronine ($rT_3$) may also be found.)
Hyperthyroidism occurring during amiodarone therapy could be serious due to coexistence of ischaemic heart disease and/or life-threatening arrhythmias in most of the patients. The risk of developing hyperthyroidism persists for at least three months after discontinuation of treatment. Patients who receive amiodarone should be instructed to consult their doctor in the event of exacerbation of angina or recurrence of tachycardia after successful therapeutic response, even when such untoward episodes occur up to six months after the drug is discontinued.

The clinical features of hypothyroidism, e.g. weight gain and reduced activity, and/or, excessive bradycardia with regard to the expected effect of amiodarone, should alert the clinician. The onset may be abrupt. The diagnosis may be supported by the presence of an elevated serum TSH level and an exaggerated TSH response to TRH. The thyroxine (T₄), T₃, and FTI may be low.

Courses of antithyroid drugs have been used for the treatment of thyroid hyperactivity; large doses may be required initially. Thyroid hypofunction may be treated cautiously with l-thyroxine.

Other:
Weight gain has occasionally been reported.

Hepatic
Elevations of hepatic enzymes may occur from time to time during therapy and are usually transient or respond to a reduction in dosage.

A few cases of acute liver disorders with high serum transaminases and/or jaundice have also been reported; in such cases treatment should be discontinued, which results in most cases in normalisation of liver function tests. However, some cases of death related to acute liver disorders have infrequently been reported.

There have also been reports of chronic liver disease (pseudo alcoholic hepatitis, cirrhosis). Clinical signs and biological changes may be minimal (possible hepatomegaly, transaminases elevated 1.5 to 5 times normal). Regular monitoring of liver function is therefore recommended during therapy. Clinical and biological abnormalities usually regress when treatment is stopped but fatal cases have been reported.

Central Nervous System
CNS effects include tremor, insomnia, headaches, dizziness, vertigo, fatigue, vivid dreams, paraesthesiae, gait abnormalities and abnormal nerve conduction.

Extrapyramidal symptoms appeared in 2 of 51 (4%) patients taking amiodarone 800 mg/day for 4 to 18 months, and in one patient given 100 mg/day for five to six days respectively.

Several cases of neuropathy indicating amiodarone induced neurolipidosis have been reported. In two studies electron microscope findings are detailed. Neuromyopathy has been reported in one patient given alternating doses of 200 to 400 mg/day and peripheral neuropathy in five patients taking between 600 and 800 mg/day for periods ranging from 4 to 18 months.

Proximal muscle weakness has been described in 4 to 6% of patients, with thigh muscle being involved in patients taking high doses (800 mg/day or more).

Other: exceptional benign intracranial hypertension (pseudotumour cerebri).

Ocular
Corneal microdeposits occur in over 90% of patients. In one study, microdeposits were present in 30% of patients at five to eight weeks, in 55% at three months and in 95% at nine months. In another study corneal deposits took eight weeks to develop but were evident in all patients.

Amiodarone keratopathy is related to dosage and duration of treatment. Patients on low doses (100 to 200 mg/day) retain clear corneas or show stage 1 changes (characterised by the coalescence of fine punctate, greyish golden brown opacities into a horizontal linear pattern in the inferior cornea). Those on high doses (400 to 1400 mg/day) develop stage 2 (characterised by additional arborising and horizontal...
lines) and stage 3 (characterised by a verticillate, whorl-like pattern) changes which are dependent on duration of treatment. The keratopathy progresses even with reduced dosage, however complete regression occurs when the drug is withdrawn. Complete clearing is reported to occur from between three and seven months after withdrawal of the drug.

Corneal microdeposits are essentially benign in nature causing no visual disturbances and have only rarely given rise to symptoms such as visual haloes.

A few cases of neuropathy/optic neuritis have been reported. At present, the relationship to amiodarone has not been formally established. If blurred or decreased vision occurs, 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.

Psychiatric
Chronic anxiety has been reported.

Respiratory
Cases of pulmonary toxicity (alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organizing pneumonia/BOOP), sometimes resulting in fatalities have been reported.

Chest X-ray should be performed in patients developing dyspnoea (at effort), or any new respiratory symptom, while taking amiodarone, whether in isolation or associated with deterioration of general health status (fatigue, weight loss, fever).

Pulmonary disorders are generally reversible following early withdrawal of amiodarone therapy. Corticosteroid therapy may also be considered. Clinical signs usually resolve within 3 to 4 weeks, followed by slower radiological and lung function improvement (several months).

A few cases of bronchospasm have been reported in patients with severe respiratory failure and especially in asthmatic patients.

A few cases of adult acute respiratory distress syndrome, sometimes resulting in death, have been observed, usually immediately after surgery (a possible interaction with high oxygen concentration may be implicated).

Less Common Reactions

Cardiovascular
Onset or worsening of arrhythmia, sometimes followed by cardiac arrest. Conduction disturbances (sinoatrial block, AV block of various degrees). Marked bradycardia or sinus arrest in patients with sinus node dysfunction and/or in elderly patients.

Dermatological
Enhanced pustular psoriasis has been observed, alopecia.

Genitourinary
Worsening of chronic renal failure and one case of symptomatic hypercalcaemia have been reported.

Haematological
There has been a single case of bone marrow depression, but cause and effect were not established. There have been rare cases of various clinical features which may suggest a hypersensitivity reaction. These include vasculitis, renal involvement with elevation of creatinine levels, thrombocytopenia. A few exceptional cases of haemolytic anaemia or aplastic anaemia have also been reported.

Immunological
Positive antinuclear antibodies and elevated immunoglobulin levels were noted in one patient with amiodarone induced pulmonary fibrosis.
Nervous System
Delay in nerve conduction.

Ocular
Interference with visual acuity has been rarely observed in association with corneal microdeposits; gritty eyes; blurred vision; itching or burning.

Endocrine
Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other
There have been reports of epididymo-orchitis, as well as some other cases of impotence. Isolated cases of angioneurotic oedema (Quincke’s oedema) and pulmonary haemorrhage have been reported.

Severe or Life-Threatening Reactions
Cardiovascular
Bradycardia, conduction disturbances; atypical ventricular tachycardia.

Respiratory
Pulmonary fibrosis and/or alveolitis.

DOSAGE AND ADMINISTRATION
Due to poor absorption and wide interpatient variability of absorption, the initial loading and subsequent maintenance dosage schedules in clinical use of the drug have to be individually titrated. 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.

Because of the effect of food on absorption, amiodarone should be administered consistently with regards to meals.

The following dosage regimen is usually effective:

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

Maintenance
After the initial period the dosage should be reduced to 200 mg daily, or less if appropriate. Rarely, the patient may require a higher maintenance dose. The scored 100 mg 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 200 mg daily.

General Considerations
The high initial dose is necessary because of the slow onset of action whilst the necessary tissue levels of amiodarone are achieved. However, excessive dosing during maintenance therapy can cause side effects, some of which are believed to be related to excessive tissue retention of amiodarone. Side effects slowly disappear as the tissue levels fall after the dosage is reduced or the drug withdrawn. If the drug is withdrawn, residual tissue bound amiodarone may persist for three to twelve months, but the likelihood of recurrence of cardiac arrhythmias during this period should be a consideration. The important factor is that the patient requires monitoring regularly to ensure that adverse effects are detected early and the dosage adjusted accordingly. It is particularly important that the minimum effective dose be used.
Use in the 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 used. Particular attention should be paid to monitoring of thyroid function.

Paediatric Usage
The safety and effectiveness of amiodarone has not been established. Therefore its use in children is not recommended.

OVERDOSAGE
Symptoms
A case of attempted suicide with amiodarone 2600 mg is reported in the literature. No clinical symptoms, change in heart rate or blood pressure were reported. The ECG revealed considerable lengthening of the QT interval and T wave inversion in the precordial leads with transient disappearance of R wave in leads V1 to V4, simulating an anteroseptal infarction.

In another case of attempted suicide with amiodarone 8 g, the only symptom reported was profuse perspiration. No signs of cyanosis, dyspnoea or decreased sensitivity were found. No clinical side effects were documented over the monitored period of three months.

Overdosage 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 should be temporarily withdrawn and if necessary beta-adrenostimulants or glucagon given.

Treatment
Gastric lavage should be employed to reduce absorption and in addition general supportive measures should be applied in the event of ingestion of a toxic dose

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.
PRESENTATION AND STORAGE CONDITIONS

Chemmart Amiodarone 200mg Tablets

White, round tablets, biconvex with one-sided score notch.

Blister packs of 30.

AUST R number: 80770.

Chemmart Amiodarone tablets are intended for oral administration. Each tablet contains amiodarone 200mg.

In addition, each tablet contains the following inactive ingredients maize starch, lactose, povidone, magnesium stearate and anhydrous colloidal silica.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
ABN 52 096 916 418
66 Waterloo Road
North Ryde NSW 2113
Australia

NAME AND ADDRESS OF THE DISTRIBUTOR

Symbion Pharmacy Services Pty Ltd
ABN 25 000 875 034
48-58 Overseas Drive
Noble Park North VIC 3174
Australia

Chemmart is a registered trade mark of Symbion Pharmacy Services Pty Ltd.

POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

Date of TGA approval: 10 December 2001

Date of most recent amendment: 9 July 2008