PRODUCT INFORMATION

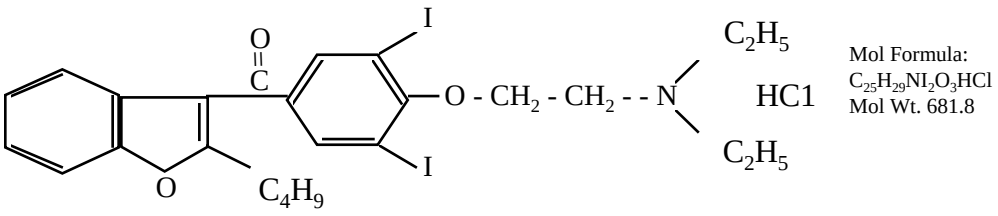
CORDARONE X 100®, CORDARONE X 200® AND CORDARONE X INTRAVENOUS®

NAME OF THE MEDICINE

Non-proprietary Name

Amiodarone hydrochloride

Chemical Structure



Mol Formula:
$C_{25}H_{29}NI_2O_3HCl$
Mol Wt. 681.8

CAS Number

1951-25-3

DESCRIPTION

Amiodarone hydrochloride is a Class III antiarrhythmic agent. The active ingredient of the Cordarone X range of products is amiodarone hydrochloride (2-n-butyl-3(4-(2-diethylaminoethoxy)-3,5-diiodobenzoyl) benzofuran hydrochloride).

Amiodarone hydrochloride is a fine white crystalline powder. It is slightly soluble in water and is soluble in alcohol and chloroform. It is an amphiphilic compound and contains iodine in its formulation. Each 200 mg tablet of amiodarone contains approximately 75 mg organic iodine and in the steady state, metabolism of 300 mg amiodarone yields 9 mg/day of iodine.

The excipients contained in each tablet are lactose, maize starch, povidone, magnesium stearate, and anhydrous colloidal silica.

The excipients contained in the intravenous solution are polysorbate 80, benzyl alcohol, and water for injections.

PHARMACOLOGY

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

Its action on ventricular arrhythmias is explained by a number of mechanisms. The effect on the atrium and A-V 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, a 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.

Atrio-Ventricular (A-V) Node:

It reduces the speed of conduction and increases the refractory period of the A-V 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.

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 inter-subject variation. First-pass metabolism in the gut wall and/or in the liver may be a factor in determining the availability of the drug.

An 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 µg/mL although inter-subject variations are common.

Considerably higher values have been reported, especially subsequent to large single doses. Peak plasma concentrations of 6.9 ± 4.2 µg/mL have been recorded following a single dose of 1600 mg and 1.7 ± 0.3 µg/mL after a single dose of 800 mg. Steady state levels of 1.57 ± 0.1 µg/mL and 3.9 µg/mL have been recorded after daily oral dosing in the range 800-1800 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 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 ie: 10 hours after a single dose of amiodarone and 60-90 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 µg/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 (200-400 mg) amiodarone 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). The concentration of amiodarone in packed red blood cells is approximately 60% of that in plasma.

INDICATIONS

Severe cases of tachyarrhythmias (eg. Wolff-Parkinson-White Syndrome, supraventricular, nodal and ventricular tachyardias, 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 (eg. thyroid function, chest X-ray, ophthalmological examination, liver function etc.) during the entire course of therapy and for several months after discontinuation.

Cordarone X Intravenous may be used for treatment initiated in a hospital for severe cases of tachyarrhythmias (atrial, junctional and ventricular) not responding to other therapy and when a rapid response is required. Cordarone X Intravenous should only be used where facilities exist for cardiac monitoring and defibrillation should the need arise.

CONTRAINDICATIONS

Known hypersensitivity to iodine or amiodarone or to any of the excipients.

Pregnancy and Lactation (see Precautions – Use in Pregnancy and Precautions – Use in Lactation).

In patients in whom bradycardia or AV block is sufficient to cause syncope, patients with sick sinus syndrome (risk of sinus arrest) or with severe atrioventricular conduction disorders, amiodarone should only be used in conjunction with a pacemaker.

Sinus bradycardia and sino-atrial heart block.

Amiodarone is contraindicated in patients with evidence, or a history of thyroid dysfunction.

Combined therapy with drugs which may induce torsades de pointes (see Precautions – Interactions with Other Medicines).

Cordarone X Intravenous injection is contraindicated in the case of hypotension, severe respiratory failure, cardiomyopathy, heart failure, circulatory collapse and severe arterial hypotension. Bi- or tri-fascicular conduction disorders, unless a permanent functioning pacemaker is fitted or, unless the patient is in a special care unit and amiodarone is used under the cover of electrosystolic pacing.

PRECAUTIONS

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

Caution should be exercised in case of hypotension, severe respiratory failure, uncompensated or severe heart failure.

Intravenous injection is generally not advised because of haemodynamic risks (severe hypotension, circulatory collapse); intravenous infusion is preferable whenever possible. Intravenous injection is to be done only in emergency where alternative therapies have failed and only in an intensive care unit under continuous monitoring (ECG, blood pressure). Intravenous injection should not be repeated less than 15 minutes following the first injection even if the latter was only one ampoule (possible irreversible collapse). To avoid injection site reactions, amiodarone IV should, whenever possible, be administrated through a central venous line (see Dosage and Administration).

Thyroid Hormone Abnormalities

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. Severe cases, with clinical presentation of thyrotoxicosis, sometimes fatal, require emergency therapeutical management.

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 thyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum 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.

Hypothyroidism should be suspected if the following clinical signs, usually slight, occur: weight gain, cold intolerance, reduced activity, excessive bradycardia. The diagnosis is supported by a clear increase in serum usTSH. Euthyroidism is usually obtained within 1 to 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.

Hyperthyroidism

Hyperthyroidism may occur during amiodarone treatment, or, up to several months after discontinuation. Clinical features, usually slight, such as weight loss, onset of arrhythmia, angina, and congestive heart failure should alert the physician. The diagnosis is supported by a clear decrease in serum ultrasensitive TSH (usTSH) level, in which case amiodarone should be withdrawn. Recovery usually occurs within a few months following withdrawal of treatment; clinical recovery precedes the normalisation of thyroid function tests. Severe and sometimes fatal cases, with clinical presentation of thyrotoxicosis, require emergency therapeutical management. The treatment should be adjusted to each individual case: for example anti-thyroid drugs, corticosteroid therapy, beta-blockers.

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.

Anaesthesia

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

Cardiac Disorders

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 onset of 2nd or 3rd degree A-V block, sinoatrial block, bifascicular or trifascicular block.

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 are more rarely reported with amiodarone than with the other antiarrhythmic agents, and generally occur in the context of drug interactions and / or electrolytic disorders (see Interactions with other Medicines).

ECG Monitoring

Regular ECG monitoring is recommended in patients on long term therapy with amiodarone. U waves, deformed T waves and QT prolongation (related to prolonged repolarisation) 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 0.60 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, etc) 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 Disorders

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 or when diagnosis is suspected. 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) such as interstitial pneumonitis. Very rare cases of interstitial pneumonitis have been reported with intravenous amiodarone. A chest X-Ray should be performed when the diagnosis is suspected, in patients developing effort dyspnoea whether isolated, or, associated with deterioration of general health status (fatigue, weight loss, fever). Amiodarone therapy should be re-evaluated since interstitial pneumonitis is generally reversible following early withdrawal of amiodarone (clinical signs usually resolving within 3 to 4 weeks, followed by slower radiological and lung pulmonary function improvement within several months), and corticosteroid therapy should be considered.

Very rare cases of severe respiratory complications, sometimes fatal, have been observed usually in the period immediately following surgery (adult acute respiratory distress syndrome); a possible interaction with a high oxygen concentration may be implicated.

Hepatic Dysfunction

Regular monitoring of liver function tests (transaminases) is recommended as soon as amiodarone is started and during treatment.

Elevation of liver enzyme (e.g. serum aspartate aminotransferase, serum alanine aminotransferase, glutamyl transpeptidase) levels 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 with liver function tests is recommended as soon as amiodarone is started and regularly during treatment.

Acute liver disorders (including severe hepatocellular insufficiency or hepatic failure, sometimes fatal) and chronic liver disorders may occur with oral and intravenous forms and within the first 24 hours of IV amiodarone. 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 (hepatomegaly, transaminases increased up to five times the normal range) and reversible after treatment withdrawal, however fatal cases have been reported.

Use in Hepatic Disease

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

Skin Reaction

Photosensitivity is quite common (see Adverse Effects - Dermatological) and there is a wide spectrum of skin reactions, ranging from an increased propensity to suntan 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) regime (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.

Use in Renal Disease

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

Hypotension

Hypotension may occur when amiodarone is given by the intravenous route. In some cases, hypotension may be refractory, resulting in fatal outcomes (see Adverse Effects - Cordarone X Intravenous).

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 foetus, its use is probably best avoided in the three months before and throughout the duration of pregnancy. Where exposure of the foetus is unavoidable, thyroid function (including TSH) 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 a 35 year old woman administered amiodarone in the last weeks of pregnancy, 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 foetal thyroid are of concern since administration of iodine (of which there are 75 mg in a 200 mg dose of amiodarone) during pregnancy may cause foetal goitre, hypothyroidism and mental retardation.

Another patient received 800 mg amiodarone for 1 week (maintenance dose thereafter was 400 mg daily) in her 34th 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.

Use in Lactation

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

Paediatric Use

The safety and efficacy of amiodarone in paediatric patients have not been established. Therefore its use in paediatric patients is not recommended.

The ampoules of amiodarone injection contain benzyl alcohol (see Description). There have been reports of fatal "gasping syndrome" in neonates (children less than one month of age) following the administration of intravenous solutions containing this preservative. Symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardiovascular collapse.

Use in the Elderly

In the elderly, heart rate may decrease markedly.

Carcinogenicity

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 man is unknown. Clinical experience has indicated that amiodarone can affect thyroid function.

INTERACTIONS WITH OTHER MEDICINES

Combined therapy with drugs that may induce 'torsades de pointes' is contraindicated (see Contraindications)**:**

Antiarrhythmic Agents, such as:

Class IA antiarrhythmic agents, including:

- Disopyramide: combined treatment of amiodarone and disopyramide causes an increase in the QT interval.
- Procainamide: serum level of procainamide increases significantly with coadministration of amiodarone and secondary to this increase cardiac, gastrointestinal and neural toxicity may develop.
- Quinidine: atypical ventricular tachycardia with QT prolongation may develop after amiodarone is 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 can increase 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: coadministration with amiodarone increases QT interval.

Sotalol

Bepridil

Non-antiarrhythmic Agents, such as: vincamine, some neuroleptic agents, cisapride, erythromycin IV or pentamidine IV, as there is an increased risk of potentially lethal 'torsades de pointes'.

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 and conduction disorders may occur.

Calcium Antagonists: coadministration of amiodarone with drugs of the calcium antagonist type may lead to undue bradycardia and conduction disorders may occur.

MAO Inhibitors: coadministration with monoamine oxidase inhibitors 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 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-); tetracosactrin; amphotericin B (IV). 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).

Digoxin: coadministration of amiodarone to patients already receiving digitalis increases plasma digoxin concentrations by about 70% this is possibly due to the decrease in digoxin clearance 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: amiodarone increases the concentration of flecainide plasma levels: the dosage of flecainide should be adjusted.

Anaesthesia, oxygen therapy (see Precautions): 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: amiodarone raises plasma concentrations of phenytoin. The combination of phenytoin and amiodarone may lead to increases 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 and other anticoagulant agents: amiodarone raises the concentration of warfarin. The combination of warfarin with amiodarone potentiates the effect of the 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.

Medicines 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.

Statins metabolised by CYP 3A4: The risk of muscular toxicity is increased by concomitant administration of amiodarone with statins metabolised by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolised by CYP 3A4 when given with amiodarone.

Other: lignocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine.

Medicines metabolised by cytochrome P450 2D6 and 2C9: amiodarone has been reported to interact with Flecainide, a CYP 2D6 substrate and Phenytoin and Warfarin which are CYP 2C9 substrates; as such amiodarone may interact with other 2D6 and 2C9 substrates.

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 2 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 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.

General

It has been shown that there is a physical incompatibility of heparin and aminophylline with amiodarone when mixed in an infusion administration set. It is recommended that amiodarone for infusion not be mixed with other drugs.

ADVERSE EFFECTS

Cordarone X Intravenous may cause moderate and transient reduction in blood pressure, and circulatory collapse may be precipitated by too rapid administration or overdosage. Atropine has been successfully used in such patients presenting with bradycardia. Temporary hot flushes, sweating, nausea have also been reported with Cordarone X Intravenous.

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 underlying disease state, and individual variation in 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 Precautions – Effect on 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 2 patients, given disopyramide and amiodarone, on withdrawal of the amiodarone, the disopyramide did not induce atypical ventricular tachycardia.

Bradycardia: marked bradycardia or sinus arrest has occasionally been reported in patients with sinus node dysfunction or elderly patients. Reports of moderate and dose related bradycardia are common.

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 sunscreen 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, during the course of radiotherapy; 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 hyper- and hypothyroidism have occurred during or soon after treatment with amiodarone. Simple monitoring of the usual biochemical tests is confusing because some (PBI and ^{131}I uptake) are invalidated and others (T4, T3 and 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, recurrence of cardiac dysrhythmia, onset of angina or congestive heart failure. The diagnosis may be confirmed by the finding of an elevated serum triiodothyronine (T3), a low level of thyroid stimulating hormone (TSH) and a reduced TSH response to thyrotropin releasing hormone (TRH). (Elevation of reverse tri iodothyronine (rT3) may also be found). Hyperthyroidism occurring during amiodarone therapy could be serious and sometimes fatal 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 3 months after discontinuation of treatment. Patients who receive amiodarone should be instructed to consult their physician in the event of exacerbation of angina or recurrence of tachycardia after successful therapeutic response, even when such untoward episodes occur up to 6 months after the drug is discontinued.

The clinical features of hypothyroidism such as weight gain, 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 free thyroxine index (FTI) may be low.

Courses of anti-thyroid 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 liver 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, including hepatic failure, 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.

Nervous System

CNS effects include tremor, insomnia, headaches, dizziness, vertigo, fatigue, sleep disorders, vivid dreams, nightmares, paraesthesia, gait abnormalities, and abnormal nerve conduction. Extrapyramidal symptoms appeared in 2 of 51 (4%) patients taking 800 mg/day of amiodarone for 4 to 18 months and in one patient given 100 mg/day for 5 to 6 days respectively.

Uncommon reports of peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the drug, have been received. 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 5 patients taking between 600 and 800 mg/day for periods ranging 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).

Ocular

Corneal microdeposits occur in over 90% of patients. In one study microdeposits were present in 30% at 5 to 8 weeks, in 55% at 3 months and in 95% at 9 months. In another study corneal deposits took 8 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 arborizing 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 3 and 7 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 coloured haloes in dazzling light or blurred vision. Corneal microdeposits consist of complex lipid deposits and are reversible following discontinuation of treatment.

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/interstital pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising 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.

Urticaria

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 was not established.

There have been rare cases of various clinical features which may suggest a hypersensitivity reaction: 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 level 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 cases of impotence.

Isolated cases of angioneurotic oedema (Quincke's oedema) and pulmonary haemorrhage have been reported. Cerebellar ataxia, benign intracranial hypertension (pseudotumour cerebri) are very rarely reported.

Serious or Life Threatening Reactions

Cardiovascular

Bradycardia, conduction disturbances; atypical ventricular tachycardia.

Respiratory

Pulmonary fibrosis and/or alveolitis.

Adverse reactions - Cordarone X Intravenous

Local

Possible inflammation of veins following intravenous infusion that may be avoided by the use of a central venous catheter. Injection site reactions such as pain, erythema, urticaria, oedema, necrosis, extravasation, infiltration, inflammation, induration, thrombophlebitis, phlebitis, cellulitis, infection, pigmentation changes.

Systemic

Hot flushes and sweating have been reported very rarely.

Common reports of decrease in blood pressure, usually moderate and transient have been received. Cases of severe hypotension or collapse (sometimes fatal) have been reported following overdosage or a too rapid injection.

Moderate bradycardia. In some cases, and especially in patients with sinus node dysfunction and/or elderly patients, marked bradycardia, or more exceptionally sinus arrest, requires the discontinuation of therapy.

Occurrence of arrhythmia, or aggravation of the pre-existing trouble, followed in some cases by cardiac arrest have been reported. In view of current knowledge, it is not possible to differentiate what may be due to the drug, from what may be related to the underlying cardiac condition, or what may be the result of a lack of efficacy of therapy. These effects are more rarely reported than with most of the other anti-arrhythmic agents and they occur in general in case of certain drug interactions or electrolyte disorders.

Isolated elevation of serum transaminases, which are usually moderate (1.5 to 3 times normal) have been reported at the beginning of therapy. They may regress with dose reduction or even spontaneously.

Very rare cases of acute liver disorders with elevated serum transaminases and/or jaundice, which included hepatic failure, sometimes fatal have also been reported. Treatment should be discontinued and monitoring of liver function tests is therefore recommended.

Very rare cases of interstitial pneumonitis have been reported with intravenous amiodarone.

Very rare cases of severe respiratory complications, sometimes resulting in death have been observed usually in the period immediately following surgery (acute adult respiratory distress syndrome), sometimes fatal: a possible interaction with high oxygen concentrations may be implicated. Bronchospasm and/or apnoea in the case of pre-existing severe respiratory failure and especially in asthmatic patients have also been reported.

Very rare cases of anaphylactic shock and benign intra-cranial hypertension (pseudotumour cerebri) have been reported.

Nausea and headache have been reported very rarely. Isolated cases of angioneurotic oedema (Quincke's oedema) have been reported.

Back pain.*

DOSAGE AND ADMINISTRATION

Due to poor absorption and wide inter-patient variability of absorption the initial loading and subsequent maintenance dosage schedules of the drug in clinical use has 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. 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 3 to 12 months, but the likelihood of re-occurrence 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.

Intravenous

Cordarone X Intravenous Injection should only be used when facilities exist for cardiac monitoring and defibrillation, should the need arise. Intravenous injection is generally not advised because of hemodynamic risks (severe hypotension, circulatory collapse). Intravenous infusion should be preferred whenever it is possible.

The standard recommended dose is 5 mg/kg body weight given by intravenous infusion over a period of 20 minutes to 2 hours. This should be administered as a dilute solution in 250 mL 5% glucose. CORDARONE X INTRAVENOUS INJECTION IS INCOMPATIBLE WITH SALINE AND SHOULD BE ADMINISTERED SOLELY IN 5% GLUCOSE SOLUTION.

When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended to avoid thrombophlebitis.

This may be followed by repeat infusions up to 1200 mg ie; 15 mg/kg body weight in up to 500 mL 5% glucose per 24 hours, the rate of infusion being adjusted on the basis of clinical response.

In extreme clinical emergency the drug may at the discretion of the clinician be given as a slow injection of 150-300 mg in 10-20 mL 5% glucose over 1-2 minutes (see Adverse Effects). Patients treated in this way must be closely monitored e.g. in an intensive care unit.

Do not mix amiodarone with other preparations in the same syringe or infusion solution.

Oral therapy should be initiated as soon as possible after an adequate response is obtained and the intravenous therapy gradually phased out and an overlap of oral and intravenous medication of up to two days is recommended to prevent plasma levels falling and efficacy being lost. Repeated or continuous infusion via the peripheral veins may lead to local discomfort and inflammation.

Ampoules in which a precipitate or cloudiness have formed should be discarded. Cordarone X Intravenous does not contain any preservative and should be prepared immediately prior to use and used within 12 hours.

When given by infusion, Cordarone X Intravenous may reduce drop size: the alteration in drop size may be equipment dependent but a reduction in drop size to two thirds has been reported. This problem may be overcome either by using a volumetric infusion pump or by adjusting the rate of infusion, however, the important criterion is clinical response and continuous monitoring of the patients physiological parameters should be carried out during infusion.

Experience has shown that amiodarone can be absorbed into PVC infusion bags and administration sets possibly because of the presence of plasticisers in PVC plastic. It is important to prepare the infusion solution immediately prior to use in either glass or rigid PVC bottles containing no plasticisers and use within 12 hours.

The use of medical equipment or devices containing plasticiser such as DEHP (di-2-ethylhexyl phthalate) in the presence of amiodarone injection may result in leaching out of DEHP. In order to minimise patient exposure to DEHP, the final amiodarone dilution for infusion may preferably be administered through non-DEHP containing sets.

Use in the Elderly

As with all patients it is important 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.

OVERDOSAGE

A case of attempted suicide with 2600 mg amiodarone is reported in the literature. No clinical symptoms, changes 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 antero-septal infarction.

In another case of attempted suicide with 8 g amiodarone, the only symptoms reported were profuse perspiration. No signs of cyanosis, dyspnoea or decreased sensitivity were found. No clinical side effects were documented over the monitored period of 3 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. In the event of ingestion of a toxic dose, gastric lavage should be employed to reduce absorption and in addition general supportive measures should be applied.

Contact the Poisons Information Centre (telephone 131126) for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Tablets

1. Cordarone X 100 - white to off-white circular tablets, scored on one side with logo on reverse side. Approximately 8.7 mm in diameter, each containing 100 mg amiodarone hydrochloride.
2. Cordarone X 200 - white to off-white circular tablets, scored on one side with logo on reverse side. Approximately 10.5 mm in diameter, each containing 200 mg amiodarone hydrochloride.

The tablets are presented blister packed in strips of 10 tablets in packs containing 30 tablets.

Store below 30^{o}C. Protect from light.

Injection

Cordarone X Intravenous is a clear, pale yellow solution for intravenous administration.

Each ampoule contains 150 mg amiodarone hydrochloride in 3 mL. The ampoules are packed in units of 6 or 10[#] on a tray contained in a cardboard carton.

Store below 25°C. Do not refrigerate.

Protect from light.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF APPROVAL

Date of first inclusion in the ARTG: 30 September 1991

Date of most recent amendment: 25 July 2011

* Changes of Clinical Significance

[#] Not marketed