DARONEX

Tablets

Composition
Each tablet contains Amiodarone 200 mg

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 medicine 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 ischemic damage or angina pectoris.

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

Myocardial Electrophysiology
Sinus Node
It decreases sinus automaticity by reducing the slow diastolic depolarization 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 depolarization 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 medicine.

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 medicine 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

Treatment should be initiated only under hospital or specialist supervision.

- Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome. Atrial flutter and fibrillation when other agents cannot be used.
- All types of tachyarrhythmias of paroxysmal nature including: supraventricular, nodal and ventricular tachycardias, ventricular fibrillation; when other agents cannot be used. Tablets are used for stabilization and long term treatment.

Contraindications

- Known hypersensitivity to iodine or Amiodarone or to any of the excipients.
- Pregnancy and 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 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 medicines which may induce torsades de pointes.

Adverse Reactions

Since the occurrence of certain side effects may be evident only after prolonged use, patients should be continually monitored.

Ophthalmological: Following continuous therapy, some patients may develop micro-deposits in the cornea.
The deposits are usually only visible by slit light examination and very rarely give rise to symptoms such as visual haloes.
These micro-deposits regress on reduction or discontinuation of Amiodarone and are considered benign in nature.
Impaired visual acuity due to optic neuritis has been observed.
Regular ophthalmological examinations are recommended during long term therapy.

Cardiac: Bradycardia which is generally moderate and dose dependant has been reported. In some cases (sinus node disease, elderly patients) marked bradycardia or sinus arrest has occurred. Rare instances of conduction disturbances (Sino-atrial block, various degrees of AV block) have been reported.

The proarrhythmic effect of Amiodarone has usually occurred in combination with other precipitating factors, particularly other antiarrhythmic agents, digoxin and hypokalemia

Dermatological: Photosensitization may be induced in certain individuals - this can usually be alleviated by the use of total sun block barrier creams and other protective measures.
Less frequently a bluish discoloration of the skin has been reported. This pigmentation is usually slowly reversible on discontinuation of Amiodarone, but may not completely disappear.

Thyroid: Both hyper- and hypothyroidism have been reported either during or soon after treatment with Amiodarone.

Monitoring of the usual thyroid tests may be confusing because some (PBI and ^{131}I uptake) are invalidated and others (T_4, T_3 and FTI), may be altered, where the patient is clearly euthyroid. Clinical monitoring is therefore recommended and should be continued for several months following discontinuation of Amiodarone therapy.

This follow up monitoring is particularly important in the elderly. In patients who have a history of thyroid dysfunction, regular testing is recommended.

Clinical features of hyperthyroidism, such as mass loss, asthenia, restlessness, increase in heart rate or the recurrence of cardiac dysrhythmia, angina or congestive heart failure, should alert the clinician. The diagnosis may be supported by an elevated serum tri-iodothyronine (T_3), a low level of thyroid stimulating hormone (TSH) and a reduced TSH response to thyrotropin releasing hormone (TRH). Elevation of reverse T_3 (rT_3) may also be found.

Clinical features of hypothyroidism such as mass gain and reduced activity or excessive bradycardia 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 thyroxin (T4) T3 and free thyroxine index may be low.

In the case of hyperthyroidism Amiodarone should be withdrawn.

In cases of severe hyperthyroidism, courses of antithyroid medication have been used and large doses are required initially. These may not always be effective and concomitant high dose corticosteroids may be required for several weeks. Thyroid hypo function usually resolves within 3 months of discontinuation of Amiodarone therapy and it may be treated cautiously with L-thyroxin.

Concomitant use of Amiodarone is only advocated in life threatening situations, when TSH levels may provide a guide to the dosage of L-thyroxin.

Pulmonary: Severe pulmonary toxicity has been reported, including fibrosis and interstitial pneumonitis. Diffuse pulmonary alveolitis may also occur, sometimes presenting as unexplained or disproportionate dyspnoea.

There may be an associated deterioration in general health (mass loss, fever, fatigue). Patients developing dyspnoea, without signs of cardiac failure or loss of control of arrhythmias, should be clinically evaluated, including lung function tests and chest X-ray.
Pulmonary alveolitis is usually reversible on early discontinuation of amiodarone use, with or without concomitant use of corticosteroids. Clinical symptoms often resolve within weeks followed by slower radiological and lung function improvement. These pulmonary effects may be potentially fatal.

Hepatic: Liver function, particularly transaminases, should be monitored before treatment and periodically thereafter. At the beginning of therapy elevation of serum transaminases which can be in isolation (1,5 to 3 times normal) may occur. These may return to normal with dose reduction or sometimes spontaneously. Occasional cases of acute liver disorders with elevated serum transaminases and / or jaundice may occur. These normally resolve once treatment has been

withdrawn.

There have been reports of chronic liver disease during long term therapy. Alteration of laboratory tests (transaminases elevated 1,5 to 3 times) or clinical signs (possible hepatomegaly), during treatment of longer than 6 months, should suggest this diagnosis. Routine monitoring of liver function tests is advised. A few cases of irreversible progression have been reported. Histological findings may resemble pseudo-alcoholic hepatitis - they can be variable and may include cirrhosis.

Neurological: Peripheral neuropathy and or myopathy. These conditions may be serious and may be reversible on withdrawal of Amiodarone.

Nightmares, vertigo, headaches and sleeplessness may occur. Tremor and ataxia have also been reported, usually with complete regression following reduction of dose or withdrawal of treatment. Benign raised intra-cranial pressure has been reported.

ECG: Amiodarone will induce ECG changes : QT interval lengthening corresponding to prolonged repolarization, U waves and deformed T waves may occur because of the fixing of Amiodarone in the cardiac tissue. These are not signs of toxicity and dosing may continue.

Other: Nausea, vomiting, metallic taste (which usually occur with loading dose and which regress on dose reduction) fatigue and epididymo-orchitis have been reported. Isolated cases suggesting hypersensitivity have been reported. Symptoms include vasculitis, renal involvement with moderate elevation of creatinine levels or thrombocytopaenia have been observed.

Warnings and Precautions

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

As Amiodarone may induce thyroid disorders, 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 therapeutic management.

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

Anaesthesia: Before surgery the anesthetist should be informed that the patient is taking Amiodarone.

Use in 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. 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, Sino-atrial block, bifascicular or trifascular block.

ECG 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 medicine. 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; Torsade 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 Lesions
Clinical and radiological evidence of pulmonary fibrosis and/or pneumonitis has been reported sometimes presenting as unexplained or disproportionate dyspnoea .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.

Pregnancy
Category D
There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing Mothers
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.

Pediatric Use
The safety and efficacy of Amiodarone in pediatric patients have not been established. Therefore its use in pediatric patients is not recommended.

Hepatic Dysfunction
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 is asymptomatic. The changes appear to be dose dependent rather than an idiosyncratic type. Hepatotoxicity has occasionally been reported and closes 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. 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.

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 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) regime.

Intracellular inclusion bodies, similar to those seen in skin have been demonstrated in peripheral nerve fibres. Sensorimotor neuropathy, with a glove and stocking distribution has been reported in patients. Histologically, segmental demyelination of the nerve fibres has also been demonstrated. After discontinuation of the medicine, the neurological complication is slowly and incompletely resolved.

Use in Renal Disease
Renal excretion of the medicine is minimal. This suggests that modification of the dose of Amiodarone in patients with renal failure is unnecessary.

Drug Interactions
Combined therapy with medicines that may induce 'Torsade de Pointes' is contraindicated.

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 levels of procainamide increased significantly with co administration 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 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, such as
Erythromycin IV & Pentamidine IV

As there is an increased risk of potentially lethal 'Torsades de Pointes.'

Combined therapy with the following medicines is not recommended
Beta adrenergic blocking medicines
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 medicines of the calcium antagonist type may lead to undue bradycardia.

MAO Inhibitors
Co administration with monoamine oxidase inhibitors is contraindicated on theoretical grounds.

Stimulant laxative agents
Their use may cause Hypokalemia 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 medicines in combination with Amiodarone:
Agents which may induce Hypokalemia
For example: diuretics inducing Hypokalemia, either alone or combined; systemic corticosteroids (gluco-, mineralo-); tetracosactrin; amphotericin B (IV). It is necessary to prevent the onset of Hypokalemia (and to correct Hypokalemia); 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
Co administration of Amiodarone 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.

Anesthesia, oxygen therapy
Potentially severe complications have been reported in patients undergoing general anesthesia, 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 and 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.

Medicines metabolised by cytochrome P450 3A4
When such medicines 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:
Cyclosporine: 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 medicines particularly those which are highly protein bound.

Interference with Clinical, Laboratory and Other Tests
Thyroid Function Tests
Amiodarone contains 2 atoms of iodine and bears a structural resemblance to the molecule of thyroxin. A 300mg 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 medicine 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 thyroxin (T4), reverse triiodothyronine (rT3) and free thyroxin 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 medicines such as Dexamethasone.

Dosage and Administration
The minimum effective dose should be used at all times. Dosage should be adjusted according to individual patient's response and well being.

The following dosage regimen is generally effective.
Initial stabilization: - initiate treatment with 200 mg three times daily for one week. Reduce this dosage to 200 mg twice daily for a further week.

Maintenance: - following the initial stabilization period, the dosage should be reduced to 200 mg daily, or less, if appropriate. The maintenance dose should be regularly reviewed, especially where this exceeds 200 mg daily.

GENERAL CONSIDERATIONS
It is necessary to administer high initial doses because the onset of action is slow, whilst the necessary tissue levels of Amiodarone are being achieved. Amiodarone has a very low acute toxicity, therefore few serious problems have been observed during this initial phase.

Excessive dosing during maintenance therapy may cause side effects which are thought to be due to excessive tissue retention of Amiodarone and / or its metabolites. The side effects gradually disappear as the tissue levels of Amiodarone decline following reduction of dosage or withdrawal of Amiodarone.

Once Amiodarone treatment is withdrawn, residual tissue bound Amiodarone may protect the patient for up to one month, but the likelihood of the reoccurrence of cardiac arrhythmias, during this

period should be considered. Patients should be regularly monitored for clinical signs of overdosage and the dosage should be adjusted accordingly.

It is most important that the minimum effective dose be used.

Use in the elderly
It is important that the minimum effective dose be used.
Whilst there is no evidence that dosage requirements are different in the elderly, they may be more susceptible to bradycardia and conduction defects if too high a dose is administered. Particular attention should be paid to monitoring thyroid function.

Overdosage

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 therapy should be withdrawn. Gastric lavage may be employed to reduce absorption, in addition to general supportive measures. Patients should be monitored and if bradycardia ensues beta adreno-stimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of Amiodarone adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended.

Storage Instructions

Store in a well closed container below 25°C, protected from light.
KEEP OUT OF REACH OF CHILDREN.
Do not remove blisters/tablets from outer container until required for use.

Presentation

Box of 30 Tablets