

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amiodarone 50 mg/ml solution for I.V. injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 ml ampoule contains 150 mg amiodarone hydrochloride.

Each ml contains 50 mg amiodarone hydrochloride.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear and has a pale yellow colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Tachyarrhythmias associated with Wolff-Parkinson-White syndrome.

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

Amiodarone 50 mg/ml solution for I.V. injection can be used where a rapid response is required or where oral administration is not possible.

4.2 Posology and method of administration

Amiodarone 50 mg/ml solution for I.V. injection should only be used when facilities exist for cardiac monitoring, defibrillation, and cardiac pacing.

Amiodarone 50 mg/ml solution for I.V. injection may be used prior to DC cardioversion.

The standard recommended dose is 5mg/kg bodyweight given by intravenous infusion over a period of 20 minutes to 2 hours. This should be administered as a dilute solution in 250ml 5% dextrose. This may be followed by repeat infusion up to 1200mg (approximately 15mg/kg bodyweight) in up to 500ml 5% dextrose per 24 hours, the rate of infusion being adjusted on the basis of clinical response (*see section 4.4*).

In extreme clinical emergency the drug may, at the discretion of the clinician, be given as a slow injection of 150-300mg in 10-20ml 5% dextrose over a minimum of 3 minutes. This should not be repeated for at least 15 minutes. Patients treated in this way with Amiodarone 50 mg/ml solution for I.V. injection must be closely monitored, e.g. in an intensive care unit. (*see section 4.4*).

Changeover from Intravenous to Oral Therapy

As soon as an adequate response has been obtained, oral therapy should be initiated concomitantly at the usual loading dose (200mg three times a day). Amiodarone 50 mg/ml solution for I.V. injection should then be phased out gradually.

Paediatric population

Due to the presence of benzyl alcohol, intravenous amiodarone is usually contraindicated in neonates and premature babies (*see section 4.3*).

No controlled paediatric studies have been undertaken. In published uncontrolled studies effective doses for children were (*see section 4.4*):

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

If needed, oral therapy may be initiated concomitantly.

Elderly

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

Cardio Pulmonary resuscitation

The recommended dose for ventricular fibrillations/pulseless ventricular tachycardia resistant to defibrillation is 300 mg (or 5 mg/kg body-weight) diluted in 20 ml 5% dextrose and rapidly injected. An additional 150 mg (or 2.5 mg/kg body-weight) IV dose may be considered if ventricular fibrillation persists.

See section 6.2 for information on incompatibilities.

4.3 Contraindications

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

Evidence or history of thyroid dysfunction. Thyroid function tests should be performed where appropriate prior to therapy in all patients.

Severe respiratory failure, circulatory collapse, or severe arterial hypotension; hypotension, heart failure and cardiomyopathy are also contra-indications when using Amiodarone 50 mg/ml solution for I.V. injection as a bolus injection.

Known hypersensitivity to iodine or to Amiodarone 50 mg/ml solution for I.V. injection, or to any of the excipients. (One ampoule contains approximately 56mg iodine).

The combination of Amiodarone 50 mg/ml solution for I.V. injection with drugs which may induce torsades de pointes is contra-indicated (*see section 4.5*).

Amiodarone 50 mg/ml solution for I.V. injection ampoules contain benzyl alcohol. There have been reports of fatal 'gaspings syndrome' in neonates (hypotension, bradycardia and cardiovascular collapse) following the administration of intravenous solution containing this preservative. Amiodarone 50 mg/ml solution for I.V. injection should not be given to neonates or premature babies unless the rhythm disturbance is life threatening and either resistant to other medication or alternative therapy is deemed inappropriate.

Pregnancy - except in exceptional circumstances (*see section 4.6*).

Lactation (*see section 4.6*).

All these above contra-indications do not apply to the use of amiodarone for cardiopulmonary resuscitation of shock resistant ventricular fibrillation.

4.4 Special warnings and precautions for use

Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children up to 3 years old.

Amiodarone 50mg/ml solution for I.V. injection should only be used in a special care unit under continuous monitoring (ECG and blood pressure).

IV infusion is preferred to bolus due to the haemodynamic effects sometimes associated with rapid injection (*see section 4.8*). Circulatory collapse may be precipitated by too rapid administration or overdosage (atropine has been used successfully in such patients presenting with bradycardia).

Repeated or continuous infusion via peripheral veins may lead to injection site reactions (*see section 4.8*). When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended.

When given by infusion Amiodarone 50mg/ml solution for I.V. injection may reduce drop size and, if appropriate, adjustments should be made to the rate of infusion.

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

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

Cardiac disorders:

Caution should be exercised in patients with hypotension, decompensated cardiomyopathy and severe heart failure (*also see section 4.3*).

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

Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances, Amiodarone 50mg/ml solution for I.V. injection treatment should be withdrawn. If necessary beta-adrenostimulants or glucagon may be given. Because of the long half-life of amiodarone, if bradycardia is severe and symptomatic the insertion of a pacemaker should be considered.

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

Respiratory, thoracic and mediastinal disorders (*see section 4.8*):

Very rare cases of interstitial pneumonitis have been reported with intravenous amiodarone. When the diagnosis is suspected, a chest X-ray should be performed.

Amiodarone therapy should be re-evaluated since interstitial pneumonitis is generally reversible following early withdrawal of amiodarone, and corticosteroid therapy should be considered (*see section 4.8*). Clinical symptoms often resolve within a few weeks followed by slower radiological and lung function improvement. Some patients can deteriorate despite discontinuing Amiodarone 50mg/ml solution for I.V. injection. Fatal cases of pulmonary toxicity have been reported.

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 (*see sections 4.5 and 4.8*).

Hepato-biliary disorders (*see section 4.8*)

Severe hepatocellular insufficiency may occur within the first 24 hours of IV amiodarone, and may sometimes be fatal. Close monitoring of transaminases is therefore recommended as soon as amiodarone is started.

Drug interactions (*see section 4.5*)

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

Increased plasma levels of flecainide have been reported with co-administration of amiodarone. The flecainide dose should be reduced accordingly and the patient closely monitored.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Combined therapy with the following drugs which prolong the QT interval is contraindicated (*see section 4.3*) due to the increased risk of torsades de pointes; for example:

- Class IA anti-arrhythmic drugs e.g. quinidine, procainamide, disopyramide.
- Class III anti-arrhythmic drugs e.g. sotalol, bretylium.
- intravenous erythromycin, co-trimoxazole or pentamidine injection.
- some anti-psychotics e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride and sertindole.
- lithium and tricyclic anti-depressants e.g. doxepin, maprotiline, amitriptyline.
- certain antihistamines e.g. terfenadine, astemizole, mizolastine.
- anti-malarials e.g. quinine, mefloquine, chloroquine, halofantrine.
- Moxifloxacin.

Fluoroquinolones

There have been rare reports of QTc interval prolongation, with or without torsades de pointes, in patients taking amiodarone with fluoroquinolones. Concomitant use of amiodarone with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contra-indicated, see above).

Combined therapy with the following drugs is not recommended:

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

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

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

Caution is advised in patients undergoing general anaesthesia, or receiving high dose oxygen therapy.

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

A few cases of adult respiratory distress syndrome, most often in the period immediately after surgery, have been observed. A possible interaction with a high oxygen concentration may be implicated.

Grapefruit juice inhibits cytochrome P450 3A4 and may increase the plasma concentration of amiodarone. Grapefruit juice should be avoided during treatment with oral amiodarone.

Drugs metabolised by cytochrome P450 3A4

When 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: Plasma levels of cyclosporin may increase as much as 2-fold when used in combination. A reduction in the dose of cyclosporin may be necessary to maintain the plasma concentration within the therapeutic range.
- Other drugs metabolised by cytochrome P450 3A4: examples of such drugs are the statins lidocaine, tacrolimus, sildenafil, fentanyl, midazolam and ergotamine.
- Simvastatin in combination with amiodarone has been associated with reports of myopathy/rhabdomyolysis (refer to manufacturer's prescribing information for simvastatin).

Flecainide

Given that flecainide is mainly metabolised by CYP 2D6, by inhibiting this isoenzyme, amiodarone may increase flecainide plasma levels; it is advised to reduce the flecainide

dose by 50% and to monitor the patient closely for adverse effects. Monitoring of flecainide plasma levels is strongly recommended in such circumstances.

Interaction with substrates of other CYP 450 isoenzymes

In vitro studies show that amiodarone also has the potential to inhibit CYP 1A2, CYP 2C19 and CYP 2D6 through its main metabolite. When co-administered, amiodarone would be expected to increase the plasma concentration of drugs whose metabolism is dependent upon CYP 1A2, CYP 2C19 and CYP 2D6.

4.6 Pregnancy and lactation

Pregnancy

There are insufficient data on the use of amiodarone during pregnancy in humans to judge any possible toxicity. However, in view of its effect on the foetal thyroid gland, amiodarone is contraindicated during pregnancy, except in exceptional circumstances.

Lactation

Amiodarone is excreted into the breast milk in significant quantities and breast-feeding is contra-indicated.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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

Cardiac disorders:

Common: Bradycardia, generally moderate.

Very rare: Marked bradycardia, sinus arrest requiring discontinuation of amiodarone, especially in patients with sinus node dysfunction and/or in elderly patients.

Onset of worsening of arrhythmia, sometimes followed by cardiac arrest (*see sections 4.4 and 4.5*).

Blood and lymphatic system disorders:

In patients taking amiodarone there have been incidental findings of bone marrow granulomas. The clinical significance of this is unknown.

Gastrointestinal disorders:

Very rare: Nausea.

General disorders and administration site conditions:

Common: Injection site reactions such as pain, erythema, oedema, necrosis, extravasation, infiltration, inflammation, induration, thrombophlebitis, phlebitis, cellulitis, infection, pigmentation changes.

Hepato-biliary disorders:

Very rare: Isolated increase in serum transaminases, which is usually moderate (1.5 to 3 times normal range) at the beginning of therapy. They may return to normal with dose reduction or even spontaneously.

Acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, sometimes fatal (*see section 4.4*).

Immune system disorders:

Very rare: Anaphylactic shock.

Nervous system disorders:

Very rare: Benign intra-cranial hypertension (pseudo tumor cerebri), headache.

Respiratory, thoracic and mediastinal disorders:

Very rare: Interstitial pneumonitis (*see section 4.4*)

Severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal (*see sections 4.4 and 4.5*)

Bronchospasm and/or apnoea in case of severe respiratory failure, and especially in asthmatic patients.

Skin and subcutaneous tissue disorders:

Very rare: Sweating.

Vascular disorders:

Common: Decrease in blood pressure, usually moderate and transient. Cases of hypotension or collapse have been reported following overdosage or a too rapid injection.

Very rare: Hot flushes.

4.9 Overdose

There is no information regarding overdosage with intravenous amiodarone.

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

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

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

Neither amiodarone nor its metabolites are dialysable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic class: Antiarrhythmics, class III

ATC code : C01BD01

5.1 Pharmacodynamic properties

Amiodarone 50 mg/ml solution for I.V. injection is a product for the treatment of tachyarrhythmias and has complex pharmacological actions. Its effects are anti-adrenergic (partial alpha and beta blockers). It has haemodynamic effects (increased blood flow and systematic/coronary vasodilation). The drug reduces myocardial oxygen consumption and has been shown to have a sparing effect of rat myocardial ATP utilisation, with decreased oxidative processes. Amiodarone inhibits the metabolic and biochemical effects of catecholamines on the heart and inhibits Na⁺ and K⁺ activated ATP-ase.

5.2 Pharmacokinetic properties

Pharmacokinetics of amiodarone are unusual and complex, and have not been completely elucidated. Absorption following oral administration is variable and may be prolonged with enterohepatic cycling. The major metabolite is desethylamiodarone. Amiodarone is highly protein bound (> 95%). Renal excretion is minimal and faecal excretion is the major route. A study in both healthy volunteers and patients after intravenous administration of amiodarone reported that the calculated volumes of distribution and total blood clearance using a two-compartment open model were similar for both groups. Elimination of amiodarone after intravenous injection appeared to be biexponential with a distribution phase lasting about 4 hours. The very high volume of distribution combined with a relatively low apparent volume for the central compartment suggests extensive tissue distribution. A bolus IV injection of 400mg gave a terminal T_{1/2} of approximately 11 hours.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Polysorbate 80

Water for Injections

6.2 Incompatibilities

Amiodarone 50 mg/ml solution for I.V. injection is incompatible with saline and should be administered solely in 5% dextrose solution. Amiodarone 50 mg/ml solution for I.V. injection, diluted with 5% dextrose solution to a concentration of less than 0.6 mg/ml, is unstable. Solutions containing less than 2 ampoules Amiodarone 50 mg/ml solution for I.V. injection in 500ml dextrose 5% are unstable and should not be used.

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

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container. Keep ampoules in the outer carton.

6.5 Nature and contents of container

Each carton contains 10 x 5ml amber glass (type I) ampoules, containing 3ml of solution.

6.6 Special precautions or disposal

Refer to 4.2 above.

After dilution in 5 % isotonic dextrose solution, the solution should be kept for maximal 8 hours at room temperature.

7. MARKETING AUTHORISATION HOLDER

O I Sciences Limited
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Long Meadow
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TQ10 9YS

8. MARKETING AUTHORISATION NUMBER

PL 33242/0003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/06/2008

10. DATE OF REVISION OF THE TEXT

16/01/2009

Legal Category

POM.