AMIODARONE 50 MG/ML SOLUTION FOR I.V. INJECTION (AMIODARONE HYDROCHLORIDE)

PL 19960/0011

UK Public Assessment Report

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PL 19960/0011

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Opal Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Amiodarone 50mg/ml solution for I.V. injection (PL 19960/0011) on 26th February 2008. This is a prescription-only medicine used to control an irregular or rapid heart rate.

Amiodarone injection contains the active ingredient amiodarone. Amiodarone is used to control an irregular or rapid heart rate when other treatments have been ineffective or cannot be used. Amiodarone injection should only be given in a hospital by a doctor.

The approved product was considered to be a generic version of the reference product Cordarone X Intravenous 150mg / 3ml solution for injection (PL 11723/0014, Sanofi-Synthelabo Limited).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Amiodarone injection outweigh the risk; hence a Marketing Authorisation (MA) has been granted.

AMIODARONE 50 MG/ML SOLUTION FOR I.V. INJECTION (AMIODARONE HYDROCHLORIDE)

PL 19960/0011

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Opal Healthcare Limited a Marketing Authorisation for the medicinal product Amiodarone 50mg/ml solution for I.V. injection (PL 19960/0011) on 26th February 2008. The product is a prescription-only medicine (POM).

The application was submitted as a standard national application, according to Article 10.1 of Directive 2001/83/EC, as amended. The application refers to the innovator product, Cordarone X Intravenous 150mg / 3ml solution for injection (PL 11723/0014, Sanofi-Synthelabo Limited) that was granted a licence on 7th March 1990.

The drug product is a solution for injection containing 50mg/ml (as 150mg / 3ml) of the active ingredient amiodarone (as amiodarone hydrochloride). Amiodarone belongs to a group of medicines called anti-arrhythmics. It is highly lipophilic and contains 37.3% iodine. The principle effect on cardiac tissue is to delay repolarisation by prolonging the action potential duration and effective refractory period.

Amiodarone is indicated for the treatment of arrhythmias, particularly when other drugs are ineffective or contraindicated. These include tachyarrhythmias associated with Wolff-Parkinson-White syndrome and all tachyarrhythmias of paroxysmal nature (supraventricular, nodal and ventricular tachycardias), atrial flutter and fibrillation, and ventricular fibrillation. The injection is to be used when a rapid response is required or where oral administration is not possible. The proposed indications for this product are the same as for the innovator product.

PHARMACEUTICAL ASSESSMENT

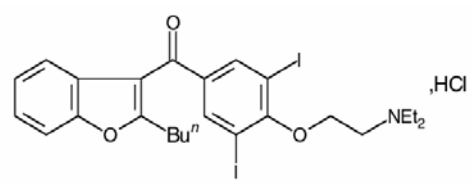
ACTIVE SUBSTANCE

Amiodarone hydrochloride

Nomenclature:

INN:	Amiodarone hydrochloride
Chemical name:	2-butylbenzofuran-3-yl-4-(2-diethylaminoethoxy)-3,5-di-iodophenyl ketone hydrochloride

Structure:



Molecular formula:	$C_{25}H_{29}I_2NO_3.HCl$
Molecular weight:	681.8
CAS No:	19774-82-4
Physical form:	A white or almost white, fine crystalline powder
Solubility:	Very slightly soluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in alcohol, very slightly soluble in hexane
Stereochemistry:	The molecule has no chiral centres.

The active substance, amiodarone hydrochloride, is the subject of a European Pharmacopeia (EP) monograph.

All aspects of the manufacture and control of amiodarone hydrochloride are supported by an EDQM Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of amiodarone hydrochloride for inclusion in this medicinal product.

Active amiodarone hydrochloride is stored in appropriate packaging that has been evaluated in relation to the grant of the CEP.

Appropriate stability data have been generated for the active substance. These data demonstrate the stability of the active substance and support a retest period of 24 months for the active substance, stored at or below 30°C, and protected from light. This is acceptable.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely benzyl alcohol, polysorbate 80, and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The benzyl alcohol has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is polysorbate 80 which has been declared as being obtained from oleic acid of animal origin. A Certificate of Suitability has been provided by the supplier of oleic acid stating that the oleic acid they provide meets the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’.

There were no novel excipients used and no overages.

Impurity profiles

Comparative impurity data were presented for a trial batch of the applicant’s product and a batch of the brand-leader product. Impurity profiles for the drug product were found to be superior to those for the reference product, and all the impurities are within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specification at release and for the product shelf life is provided. It is based on the European Pharmacopeia monograph for ‘amiodarone hydrochloride’ and the British Pharmacopeia monograph for ‘sterile amiodarone concentrate’, and is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The drug product is presented in 5ml capacity amber-coloured Type I glass ampoules containing 3ml solution. The ampoules satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. The ampoules are packaged with the Patient Information Leaflet (PIL) and technical leaflet into a cardboard outer carton, as packs of 10.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, with storage instructions ‘Do not store above 25°C’, ‘Store in the original package.’ And ‘Keep the ampoules in the outer carton’. This is satisfactory. After dilution in 5 % isotonic dextrose solution, the solution should be kept for a maximum of 8 hours at room temperature.

Bioequivalence Study

Bioequivalence studies are not necessary to support this application for a parenteral product.

EXPERT REPORT

The quality overview is written by an appropriately qualified expert and is satisfactory. A satisfactory Curriculum Vitae has been provided for the pharmaceutical expert.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory.

Conclusion

The proposed product has been shown to be a generic version of the reference product, with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

The quality grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted.

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Amiodarone 50mg/ml solution for I.V. injection is indicated for the treatment of arrhythmias, specifically when other drugs are ineffective or contraindicated. These include tachyarrhythmias associated with Wolff-Parkinson-White syndrome and all tachyarrhythmias of paroxysmal nature (supraventricular, nodal and ventricular tachycardias), atrial flutter and fibrillation, and ventricular fibrillation. The injection is to be used when a rapid response is required or where oral administration is not possible.

The indications for this product are consistent with those for the innovator product.

CLINICAL PHARMACOLOGY

No new data are submitted and none are required for this type of application.

EFFICACY

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical expert report

Amiodarone 50mg/ml solution for I.V. injection is to be administered as an intravenous solution and contains the same active substance, in the same concentration, as the currently authorised reference product Cordarone. Thus, in accordance with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence”, (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

SAFETY

No new data are submitted and none are required for this type of application. Safety is reviewed in the clinical expert report. The safety profile of amiodarone is very well defined.

EXPERT REPORT

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the innovator product and is satisfactory.

Patient Information Leaflet / Technical Information Leaflet

The approved PIL and technical leaflet are in line with the final SmPC and are satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

CONCLUSION

The grounds for establishing the proposed product as a generic version of the reference product, Cordarone X Intravenous 150mg / 3ml solution for injection (PL 11723/0014), are considered adequate. The product literature is approved.

All issues have been adequately addressed by the applicant and sufficient clinical information has been submitted to support this application. When used as indicated, Amiodarone 50mg/ml solution for I.V. injection has a favourable benefit-to-risk ratio. Therefore, a Marketing Authorisation may be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Amiodarone 50mg/ml solution for I.V. injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

The applicant's Amiodarone 50mg/ml solution for I.V. injection has been demonstrated to be a generic version of the reference product Cordarone X Intravenous 150mg / 3ml solution for injection (PL 11723/0014).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SmPC, PIL, technical leaflet, and labelling are satisfactory and consistent with that for the innovator product.

The Marketing Authorisation Holder has provided a commitment to update the Marketing Authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with amiodarone hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

AMIODARONE 50 MG/ML SOLUTION FOR I.V. INJECTION (AMIODARONE HYDROCHLORIDE)

PL 19960/0011

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 30th October 2003

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 14th January 2004

3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 5th July 2004 and further information relating to the clinical dossier on 28th July 2004

4 The applicant responded to the MHRA's requests, providing further information for the quality and clinical sections on 14th February 2005

5 Following assessment of the response the MHRA requested further information relating to the clinical sections on 17th February 2005 and for the quality sections on 8th April 2005

6 The applicant responded to the MHRA's request, providing further information for the quality and clinical sections on 4th January 2006

7 Following assessment of the response the MHRA requested further information relating to the quality sections on 9th January 2006

8 The applicant responded to the MHRA's request, providing further information for the quality sections on 2nd May 2007

9 The application was determined on 26th February 2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Amiodarone 50 mg/ml solution for I.V. injection is as follows:

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*)

<u>Changeover from Intravenous to Oral Therapy</u>

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.

<u>Paediatric population</u>

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 'gasping 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.

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 contra-indicated (*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.

<u>Fluoroquinolones</u>

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:

- Ciclosporin: Plasma levels of ciclosporin may increase as much as 2-fold when used in combination. A reduction in the dose of ciclosporin 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 (> = 10%), common (> = 1% and < 10%), uncommon (> = 0.1% and < 1%), rare (> = 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 arrythmia, 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

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic class: Antiarrhythmics, class III, ATC code : C01BD01

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 T½ 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 FOR 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

Opal Healthcare Limited
Kingswood Court Business Park
Long Meadow
South Brent
Devon
TQ10 9YS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 19960/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/02/2008

10 DATE OF REVISION OF THE TEXT

26/02/2008

PATIENT INFORMATION LEAFLET

Amiodarone 50mg/ml solution for IV injection

Each 3ml ampoule contains 150mg of Amiodarone hydrochloride Opal Healthcare Ltd.

PATIENT INFORMATION LEAFLET

Read this entire leaflet carefully before you start taking this medicine.

Keep this leaflet. You may need to read it again.

If you have further questions, please ask your doctor or your pharmacist.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet

1. What Amiodarone Injection is and what it is given for.
2. Before you are given Amiodarone Injection.
3. How Amiodarone Injection is given.
4. Possible side effects.
5. Storing Amiodarone Injection.

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

The active substance is amiodarone (as hydrochloride).

The other ingredients are benzyl alcohol, polysorbate 80 and water for injections.

Marketing authorisation holder

Opal Healthcare Limited
Kingswood Court Business Park
Long Meadow
South Brent
Devon
TQ10 9YS UK

Manufacturer

Haupt Pharma Livron
1, rue Comte de Sinard BP 1
26250 Livron
France

Product licence number

PL 19960/0011

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1. WHAT AMIODARONE INJECTION IS AND WHAT IT IS GIVEN FOR

Each ampoule contains 150mg amiodarone; this is 50mg per ml solution. Each ampoule contains 3 ml solution for injection. There are 10 ampoules in one carton. The solution is clear and has a pale yellow colour.

Amiodarone is used to control an irregular or rapid heart rate when other treatments have been ineffective or cannot be used. This type of medicine is known as an anti-arrhythmic.

Amiodarone Injection should only be given in a hospital by a doctor. It can be used where a rapid response is required. Your blood pressure and heart rate should be monitored whilst receiving Amiodarone Injection.

2. BEFORE YOU ARE GIVEN AMIODARONE INJECTION

Amiodarone Injection should NOT be given to you:

If you suffer from problems with your heart, such as heart block, which can cause a slow heart rate, a slow pulse or dizziness.

If you have or have had thyroid problems. (Your doctor will test your thyroid before prescribing this medicine).

If you have serious breathing difficulties

If you have very low blood pressure (dizziness or feeling faint at times).

If it is given as a single injection and you have serious breathing difficulties, low blood pressure, heart failure or cardiomyopathy (weakness of the heart muscle).

If you have an allergy to amiodarone, iodine or any of the other ingredients.

If you are pregnant or likely to become pregnant, except in exceptional circumstances.

If you are breast-feeding.

If you are taking certain other medicines such as:

- some other heart drugs (e.g. beta-blockers such as sotalol);
- antibiotics (e.g. erythromycin injection, co-trimoxazole or moxifloxacin);
- medicines to treat mental illness (antipsychotics, e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride and sertindole; or antidepressants, including lithium and tricyclic antidepressants e.g. doxepin, maprotiline, amitriptyline);
- medicines to treat allergic reactions (antihistamines, e.g. terfenadine, mizolastine);
- medicines to treat or prevent malaria (antimalarials);
- pentamidine injections (used to treat e.g. AIDS or pneumonia);
- stimulant laxatives.

You must inform your doctor if you are taking any of these medications.

Grapefruit juice can increase the blood level of Amiodarone Injection and should be avoided during treatment with Amiodarone 50mg/ml solution for IV injection.

Amiodarone Injection should be given to you with CARE:

If it is being given as an infusion and you have low blood pressure, severe heart failure or severe cardiomyopathy *(weakness of the heart muscle)*;

If you are going to have an anaesthetic or high dose oxygen therapy;

If you suffer from asthma or any other breathing disorder;

If you suffer from liver disease.

Pregnancy

Your doctor will prescribe Amiodarone Injection only if he/she considers the benefit of treatment outweighs the risks during your pregnancy.

Breast-feeding

You should not be given Amiodarone Injection if you are breast-feeding.

Premature and newborn babies

Amiodarone Injection should only be given to premature babies and newborns up to 1 month old if they have a heart rate disorder that is life-threatening and other treatment does not work, or is not possible. Amiodarone Injection should only be used in a special care unit under continuous monitoring (ECG and blood pressure).

Children up to 3 years old

The benzyl alcohol in this product may cause toxic and allergic reactions in infants and children up to 3 years old.

Driving and using machines

This medicine should not affect your ability to drive. However, if you experience any dizziness, make sure that you are fit to drive or operate machinery before attempting to do so.

Taking other medicines

Before Amiodarone Injection is given to you, please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine - even those which your doctor has not prescribed for you, but which you have bought yourself from your chemist/pharmacy.

In particular, please check with your doctor if you are taking any of the following, (in addition to the drugs listed in section 2, 'Before you are given Amiodarone Injection'):

- Digoxin (used to treat certain heart conditions);
- anticoagulants (used to thin the blood e.g. warfarin);
- Phenytoin (used to treat epilepsy);
- some calcium channel inhibitors (used to treat high blood pressure and angina e.g. verapamil, diltiasem);
- Ciclosporin (used after transplant operations);
- Simvastatin or other statins (used to lower cholesterol levels);
- other drugs like lidocaine, tacrolimus, sildenafil, fentanyl, midazolam and ergotamine;
- Flecainide (used to treat irregular heart rhythms);
- Fluoroquinolones e.g. ciprofloxacin (antibiotics used to treat a wide range of infections);
- drugs which may change the levels of potassium or magnesium in your blood: e.g. diuretics (water tablets), steroid tablets or the antifungal amphotericin (when given directly into a vein).

3. HOW AMIODARONE INJECTION IS GIVEN

Amiodarone Injection should only be given in a hospital by a doctor. Your blood pressure and heart rate should be monitored whilst receiving Amiodarone Injection.

Amiodarone Injection is given directly into the blood stream using a drip (or central line). It should not be given too rapidly.

This medicine is given diluted in a sugar (5% dextrose) solution.

The usual dose of Amiodarone Injection is 5 mg for every kg body weight, given by intravenous infusion over 20 minutes to 2 hours. This may then be followed by further infusions up to 1200 mg in 24 hours.

The correct dose and dilution for you will have been decided by the doctor and will depend upon your condition.

Children and the elderly may be prescribed lower doses.

IV injection may be given at an initial dose at 5mg for every kg body weight. This dose should be given over a minimum of 3 minutes and should not be repeated less than 15 minutes after initial dose. This dose regimen may be considered only in exceptional circumstances and emergencies.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Amiodarone Injection can have side effects. The side effects mentioned here have been divided into how often they occur according to the following frequencies:

Very common:	affects more than 1 in 10 people.
Common:	affects more than 1 in 100 people, but less than 1 in 10 people.
Uncommon:	affects more than 1 in 1,000 people, but less than 1 in 100 people.
Rare:	affects more than 1 in 10,000 people, but less than 1 in 1,000 people.
Very rare:	affects more than 1 in 10,000 people.

If you experience any of the following side effects you should tell your doctor immediately, who will decide whether to stop the medication.

The most common potentially serious side effects include:

- a slow pulse
- a decrease in blood pressure, leading to collapse

Other common side effects are:

- local injection site reactions including swelling, pain, redness, infection and pigmentation (skin colouring) changes

Other very rare but potentially serious side effects reported with Amiodarone Injection include:

- chest pain or palpitations (irregular heart beat), or abnormal heart rhythm or cardiac arrest
- liver disorders, including jaundice (yellowing of the skin or eyes), and may lead to liver failure
- generalised allergic reactions such as swelling of the face lips and/or tongue, shortness of breath which may be fatal
- breathing difficulties (with or without fever), inability to breath
- wheezing and breathing difficulties in patients with asthma
- bone marrow disorders
- raised pressure around the brain causing headaches and visual disturbance

Very rare and less serious side effects reported include:

- hot flushes, sweating
- nausea (feeling sick)
- headaches

If you notice any side effect not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING AMIODARONE INJECTION

Keep all medicines out of the reach and sight of children.

Do not use Amiodarone Injection after the expiry date, which is marked on both the outer carton and on each ampoule.

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

Date of preparation of leaflet: December 2007.

MEDICAL INFORMATION LEAFLET

Amiodarone 50mg/ml solution for IV injection

Each 3ml ampoule contains 150mg of Amiodarone hydrochloride Opal Healthcare Ltd.

TECHNICAL INFORMATION LEAFLET

INFORMATION FOR THE DOCTOR

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3ml ampoule contains 150mg amiodarone hydrochloride.
Each ml contains 50mg 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 50mg/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 50mg/ml solution for I.V. injection should only be used when facilities exist for cardiac monitoring, defibrillation, and cardiac pacing.

Amiodarone 50mg/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 50mg/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 50mg/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 50mg/ml solution for I.V. injection as a bolus injection.

Known hypersensitivity to iodine or to Amiodarone 50mg/ml solution for I.V. injection, or to any of the excipients. (One ampoule contains approximately 55mg iodine).

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

Amiodarone 50mg/ml solution for I.V. injection ampoules contain benzyl alcohol. There have been reports of fatal 'gasping 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).

I.V. 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.

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 I.V. 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 contra-indicated *(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 I.V. 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:

- Ciclosporin: Plasma levels of ciclosporin may increase as much as 2-fold when used in combination. A reduction in the dose of ciclosporin 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 (> = 10%), common (> = 1% and < 10%), uncommon (> = 0.1% and < 1%), rare (> = 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 arrythmia, 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 50mg/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 (> 96%). 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 I.V. injection of 400mg gave a terminal T½ 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 50mg/ml solution for I.V. injection is incompatible with saline and should be administered solely in 5% dextrose solution. Amiodarone 50mg/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 50mg/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-ethylhexylphthalate) 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 Instructions for use and handling
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
Opal Healthcare Limited, Kingswood Court Business Park,
Long Meadow, South Brent, Devon, TQ10 9YS, UK

8. MARKETING AUTHORISATION NUMBER
PL 19960/0011

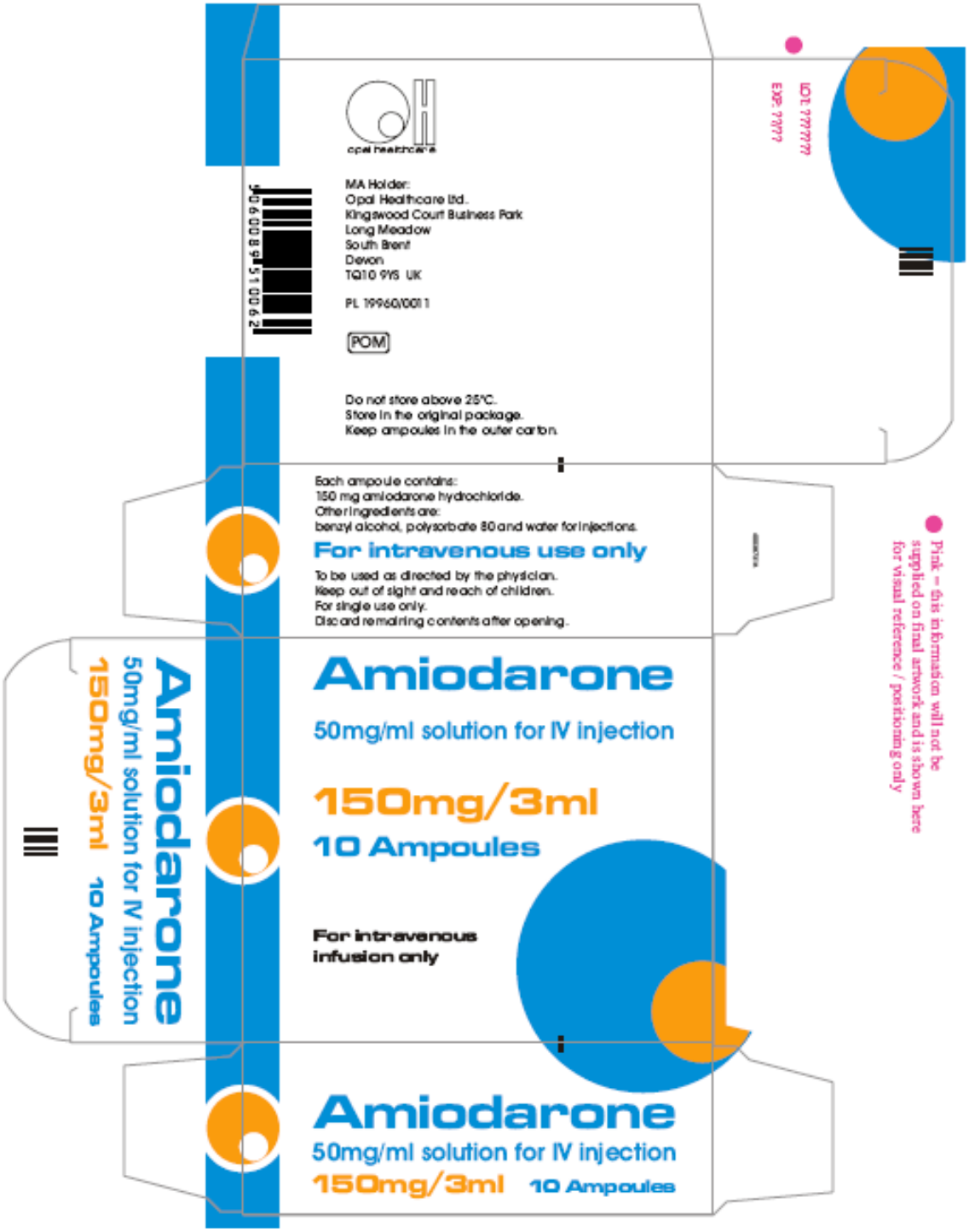
9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
November 2007

Legal Category
POM.

LABELLING

Carton



Ampoule label