Amiodarone 50mg/ml Sterile Concentrate

(amiodarone hydrochloride)

PL 18157/0008

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Beacon Pharmaceuticals Ltd a Marketing Authorisation (licence) for the medicinal product Amiodarone 50mg/ml Sterile Concentrate (PL 18157/0008) on 7th April 2011. This is a prescription-only medicine (POM).

Amiodarone belongs to a group of medicines called anti-arrhythmics, which are used to control irregular heart rhythms. Amiodarone 50mg/ml Sterile Concentrate is used to treat certain types of heart conditions, particularly when the heart is beating unevenly or much too rapidly. It is a sterile solution which is diluted before being given as an infusion (drip) into a vein.

The proposed product was considered to be a generic version of the UK reference product Cordarone X Intravenous (PL 04425/0643, Sanofi-aventis) based on the data submitted by Beacon Pharmaceuticals Ltd.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of Amiodarone 50mg/ml Sterile Concentrate outweigh the risks; hence a Marketing Authorisation has been granted.

Amiodarone 50mg/ml Sterile Concentrate

(amiodarone hydrochloride)

PL 18157/0008

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Beacon Pharmaceuticals Ltd a Marketing Authorisation for the medicinal product Amiodarone 50mg/ml Sterile Concentrate (PL 18157/0008) on 7th April 2011. The product is a prescription-only medicine (POM).

This is a generic application for Amiodarone 50mg/ml Sterile Concentrate, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The application refers to the UK reference (innovator) product, Cordarone X Intravenous, originally licensed to Sanofi UK Ltd (PL 00623/0012) on 7th March 1983. The reference licence has undergone Change of Ownership (CoA) procedures and was authorised to the current MA Holder, Sanofi-aventis (PL 04425/0643) on 31st July 2010. The innovator product has been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

Treatment with this product should be initiated and monitored 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 Sterile Concentrate can be used where a rapid response is required or where oral administration is not possible.

Amiodarone belongs to the pharmacotherapeutic group of anti-arrythmics (ATC code C01B D01). It is a product for the treatment of tachyarrhythmias and has complex pharmacological actions. Its effects are anti-adrenergic (partial alpha and beta blocker). 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.

The medicinal product is presented as a sterile, clear, colourless or pale yellow concentrate for solution for infusion. Amiodarone 50mg/ml Sterile Concentrate is incompatible with saline and should be administered solely in 5% Dextrose solution. This medicine is not for self-administration; it will be administered to the patient by a healthcare professional.

No new non-clinical or clinical studies were conducted, which is acceptable given that this is a generic application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market.

PHARMACEUTICAL ASSESSMENT

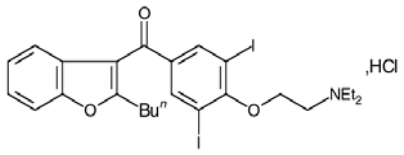
ACTIVE SUBSTANCE

Amiodarone hydrochloride

Nomenclature:

INN:	Amiodarone hydrochloride
Chemical names:	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 g/mol
CAS No:	1951-25-3
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.

The active substance, amiodarone hydrochloride, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of amiodarone hydrochloride are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of amiodarone hydrochloride for inclusion in this medicinal product.

The Certificate of Suitability specifies that the retest period of the active substance is 5 years when stored in the proposed commercial packaging.

MEDICINAL PRODUCT

Description & Composition

Amiodarone 50mg/ml Sterile Concentrate is presented in 3 ml glass ampoules as a sterile, clear, colourless or pale yellow concentrate for solution for infusion. Each 3 ml ampoule contains 150mg amiodarone hydrochloride.

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 monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to develop a generic, qualitatively identical version of the reference product, Cordarone X Intravenous (PL 04425/0643, Sanofi-aventis).

Comparative impurity data were provided for batches of the test products and appropriate reference products. The impurity profiles were satisfactory.

Manufacture

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

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

Finished product specification

The finished product specifications are provided for both release and shelf-life and are 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. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Amiodarone 50mg/ml Sterile Concentrate is presented in 3 ml colourless type I glass ampoules as a sterile concentrate for solution for infusion. The ampoules are packaged, with the product information leaflet, into cardboard outer cartons in pack

sizes of 5, 10 or 50 ampoules. The MAH has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. The ampoules satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been set. Storage instructions are 'Do not store above 25°C. Keep ampoules in the outer carton'.

Amiodarone 50mg/ml Sterile Concentrate is incompatible with saline and should be administered solely in 5% Dextrose solution. Solutions containing less than 2 Amiodarone 50mg/ml ampoules 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.

Bioequivalence Study

A bioequivalence study is not necessary to support this application for a parenteral product.

Quality Overall Summary

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

PRODUCT INFORMATION:

The approved Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided.

The PIL user testing report has been evaluated and is accepted.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. There are no objections to approval of Amiodarone 50mg/ml Sterile Concentrate from a pharmaceutical point of view.

NON-CLINICAL ASSESSMENT

This abridged application, submitted under Article 10(1) of Directive 2001/83/EC, as amended, is for Amiodarone 50mg/ml Sterile Concentrate, claiming to be a generic medicinal version of Cordarone X Intravenous (PL 04425/0643, Sanofi-aventis).

No new non-clinical data have been supplied with this application and none are required for applications of this type.

A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

CLINICAL ASSESSMENT

INDICATIONS

Treatment with this product should be initiated and normally monitored 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 Sterile Concentrate can be used where a rapid response is required or where oral administration is not possible.

The indications are consistent with those of the innovator product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the innovator product and is satisfactory.

TOXICOLOGY

The toxicology of amiodarone hydrochloride is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of amiodarone hydrochloride is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

EFFICACY

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of amiodarone hydrochloride is well-established from its extensive use in clinical practice.

Amiodarone 50mg/ml Sterile Concentrate is to be administered as an intravenous solution and contains the same active substance, in the same concentration, as the UK reference product, Cordarone X Intravenous (Sanofi-aventis). Thus, in accordance with the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), 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. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of amiodarone hydrochloride is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product and is acceptable.

Patient Information Leaflet (PIL)

The final PIL is in line with the approved SmPC and is satisfactory. The PIL user testing has been evaluated and is accepted.

Labelling

The labelling is satisfactory.

Clinical overview

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSION

Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Amiodarone 50mg/ml Sterile Concentrate 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.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

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

The applicant's Amiodarone 50mg/ml Sterile Concentrate has been demonstrated to be a generic version of the innovator product, Cordarone X Intravenous (PL 04425/0643, Sanofi-aventis).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

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

A mock-up PIL has been provided. The PIL is in line with the SmPC and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC (as amended). The results show that the leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's Amiodarone 50mg/ml Sterile Concentrate and the reference product, Cordarone X Intravenous (Sanofi-aventis), are interchangeable. Extensive clinical experience with amiodarone hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.

Amiodarone 50mg/ml Sterile Concentrate

(amiodarone hydrochloride)

PL 18157/0008

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 29th January 2003

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 15th April 2003

3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 29th May 2003 and further information relating to the quality dossier on 27th June 2003, 22nd April 2004, 27th August 2004, 19th April 2005, 9th January 2006, 23rd February 2009, 26th May 2010, 23rd August 2010 and 26th January 2011

4 The applicant responded to the MHRA's requests, providing further information for the clinical sections on 3rd February 2004 and further information for the quality sections on 3rd February 2004, 4th August 2004, 29th March 2005, 5th July 2005, 17th December 2008, 19th April 2010, 12th August 2010, 10th January 2011 and 5th April 2011 respectively

5 The application was determined on 7th April 2011

Amiodarone 50mg/ml Sterile Concentrate

(amiodarone hydrochloride)

PL 18157/0008

STEPS TAKEN AFTER AUTHORISATION

Not applicable

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Amiodarone 50mg/ml Sterile Concentrate is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Amiodarone 50mg/ml Sterile Concentrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3ml ampoule contains 150mg amiodarone hydrochloride.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment should be initiated and normally monitored 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 Sterile Concentrate 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 Sterile Concentrate should only be used when there are facilities for cardiac monitoring, defibrillation, and cardiac pacing.

Amiodarone 50mg/ml 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. A repeat infusion of up to 1200mg (approximately 15mg/kg bodyweight) in up to 500ml 5% dextrose per 24 hours may be required, the rate of infusion being adjusted on the basis of clinical response (see 4.4 Special Warnings).

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 must be closely monitored, e.g. in an intensive care unit (see 4.4 Special Warnings).

Changeover from Intravenous to Oral Therapy

When an adequate response is achieved, oral therapy should be initiated concomitantly at the usual loading dose (200mg three times a day). Amiodarone 50mg/ml should then be phased out gradually.

Children

Amiodarone 50mg/ml Sterile Concentrate should normally be given under the supervision of a paediatric cardiologist (see 4.3 contraindications).

Due to the presence of benzyl alcohol, intravenous amiodarone is usually contraindicated in neonates and premature babies.

No controlled paediatric studies have been undertaken. In published uncontrolled studies effective doses for children were:

• 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 4.3 Contraindications, 4.4 Special Warnings and 4.8 Undesirable Effects).

Cardiopulmonary resuscitation

The recommended dose for ventricular fibrillations/pulseless ventricular tachycardia resistant to defibrillation is 300 mg (or 5 mg/kg bodyweight) 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 are contraindicated. In patients with severe conduction disturbances (high grade AV block, bifascicular or trifascicular block) or sinus node disease, Amiodarone 50mg/ml should be used only in conjunction with a pacemaker.

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

Severe respiratory failure, circulatory collapse, or severe arterial hypotension; hypotension, heart failure and cardiomyopathy are also contraindications when using Amiodarone 50mg/ml Sterile Concentrate as a bolus injection.

Known hypersensitivity to iodine or to amiodarone, or to any of the excipients. (One ampoule contains approximately 56mg iodine).

The combination of amiodarone with drugs that may induce torsades de pointes is contra-indicated (see section 4.5 Interactions).

Amiodarone 50mg/ml Sterile Concentrate is contraindicated in infants or young children up to 3 years old, unless the rhythm disturbance is life threatening and either resistant to other medication or alternative therapy is deemed inappropriate. Amiodarone 50mg/ml Sterile Concentrate contains 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.

Pregnancy - except in exceptional circumstances (see section 4.6)

Lactation (see 4.6 Lactation)

All these above contraindications 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.

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

Amiodarone 50mg/ml Sterile Concentrate should only be used in a special care unit under continuous monitoring (ECG and blood pressure).

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

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

Before surgery, the anaesthetist should be informed that the patient is taking amiodarone (see 4.5 Interactions).

Cardiac disorders

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, treatment with Amiodarone 50mg/ml 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.

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

Amiodarone induces ECG changes: QT interval lengthening corresponding to prolonged repolarisation with the possible development of U and deformed T waves; these changes are evidence of its pharmacological action and 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. 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 highly protein bound drugs, for example 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 lead to 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 4.3 Contraindications) 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

• anti-psychotics e.g. chlorpromazine, thioridazine, pimozide, haloperidol, fluphenazine, amisulpiride 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 amiodrone with fluoroquinolones. Concomitant use of amidarone with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contraindicated, see above).

Combined therapy with the following drugs is not recommended:

• Beta blockers and certain calcium channel inhibitors (diltiazem, verapamil) as 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 that may cause hypokalaemia and/or hypomagnesaemia: 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.

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

• Other drugs metabolised by cytochrome P450 3A4: examples of such drugs are the statins, lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine and ergotamine.

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 contraindicated.

4.7 Effects on ability to drive and use machines

Not relevant for patients receiving intravenous amiodarone.

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%); not known (cannot be estimated from the available data).

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.

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)*.

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.

• angioedema (there have been some reports of angioedema, although exact frequencies are not known)

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.

Not known:

• urticaria.

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 oral 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 group: Antiarrythmic (Class III)

ATC code: C01B D01

Amiodarone is a product for the treatment of tachyarrhythmias and has complex pharmacological actions. Its effects are anti-adrenergic (partial alpha and beta blocker). 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 preclinical safety data which could be of relevance to the prescriber and which are not already included in other relevant sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol, Polysorbate 80 and Water for Injections.

6.2 Incompatibilities

Amiodarone 50mg/ml Sterile Concentrate is incompatible with saline and should be administered solely in 5% Dextrose solution. Solutions containing less than 2 Amiodarone 50mg/ml ampoules 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

Two years

6.4 Special precautions for storage

Do not store above 25ºC.

Keep ampoules in the outer carton

6.5 Nature and contents of container

3ml ampoules of neutral colourless type I glass

6.6 Special precautions for disposal

Refer to 4.2 above.

7 MARKETING AUTHORISATION HOLDER

Beacon Pharmaceuticals Ltd.
85 High St.
Tunbridge Wells
Kent TN1 1YG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 18157/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/04/2011

10 DATE OF REVISION OF THE TEXT

07/04/2011

PRODUCT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE PATIENT

Amiodarone 50mg/ml Sterile Concentrate

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.

In this leaflet:

1. WHAT AMIODARONE IS AND WHAT IT IS USED FOR

The active substance is amiodarone hydrochloride. Amiodarone belongs to a group of medicines called anti-arrhythmics, which are used to control irregular heart rhythms.

Amiodarone 50mg/ml Sterile Concentrate is used to treat certain types of heart conditions particularly when the heart is beating unevenly or much too rapidly. It is a sterile solution which is diluted before being given as an infusion (drip) into a vein.

2. BEFORE YOU ARE GIVEN AMIODARONE

You should NOT be given Amiodarone in the following circumstances, tell your doctor if:
- you are hypersensitive (allergic) to amiodarone hydrochloride, iodine or to any of the other ingredients (listed in section 6)
- you have certain heart problems such as a very slow heart beat (sinus bradycardia)
- you have heart failure or heart muscle disease (cardiomyopathy)
- you have severe problems with your blood circulation or very low blood pressure
- you have or have previously had thyroid problems
- you have severe breathing problems
- you are taking certain other medicines that could affect your heart beat (see 'Taking other medicines' below)
- you are pregnant or breast-feeding

Amiodarone should not be given to babies or children below 3 years of age (see, Information about some of the ingredients, overleaf).

Tell your doctor if:
- you have low blood pressure
- you are to undergo a general anaesthetic
- you require oxygen treatment.

Taking other medicines

Tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Amiodarone should NOT be given and you should tell your doctor if you are taking any of the following:
- medicines which may cause a heart condition called Torsades de Pointes (heart rhythm disturbance), these include:
  - other antiarrhythmic medicines e.g. quinidine, procainamide, disopyramide, sotalol, bretylium
  - antibiotic injections e.g. erythromycin, co-trimoxazole, moxifloxacin or pentamidine
  - medicines used to treat mental illness e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpiride, sertindole
  - lithium and tricyclic antidepressants e.g. doxepin, maprotiline, amitriptyline
  - antihistamines, used to treat allergies and hayfever e.g. terfenadine, astemizole, mizolastine
  - anti-malarial medicines e.g. quinine, mefloquine, chloroquine, halofantrine.

Tell your doctor if you are taking any of the following, as amiodarone may interact with them:
- antibiotics e.g. ciprofloxacin, ofloxacin, levofloxacin
- warfarin used to thin the blood
- digoxin, taken for heart problems
- phenytoin, most often used to treat epilepsy
- some medicines used to treat heart problems or high blood pressure e.g. betablockers, verapamil, diltiazem
- laxatives e.g. bisacodyl, senna
- some diuretics (water tablets) e.g. furosemide
- corticosteroids used for inflammation
- tetracosactide used in some blood tests or sometimes in the treatment of Crohn's disease or hormone problems
- flecainide used to treat arrhythmias
- amphotericin injection used for fungal infections
- ciclosporin or tacrolimus used to prevent transplant rejection
- statins used to lower cholesterol e.g. simvastatin
- medicines for impotence e.g. sildenafil
- fentanyl used for pain relief
- dihydroergotamine or ergotamine for migraine
- midazolam used to relieve anxiety
- triazolam, a sedative used to treat insomnia
- lidocaine, an anaesthetic.

Continued overleaf .....

Information for the Healthcare Professional
Amiodarone 50mg/ml Sterile Concentrate
Please read full prescribing information contained in the Summary of Product Characteristics.
Presentation: Each ampoule contains 150mg amiodarone hydrochloride in 3 ml of clear colourless solution. **Dosage and Method of Administration**: The standard recommended dose is 5mg/kg bodyweight given by i.v. infusion over a period of 20 minutes to 2 hours, 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 to the clinical response. In extreme clinical emergency the drug may, 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 must be closely monitored. When 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 should then be phased out gradually.
Children: Amiodarone Concentrate should normally be given under the supervision of a paediatric cardiologist. Due to the presence of benzyl alcohol, i.v. amiodarone is usually contraindicated in neonates and premature babies and in children up to 3 years. In published uncontrolled studies effective doses for children were:
• 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.

Pregnancy and breast-feeding
Amiodarone should not be given if you are pregnant, think you might be pregnant or are breast-feeding. Talk to your doctor before this medicine is given.

Important information about some of the ingredients
This medicine contains benzyl alcohol (20.2mg/ml), which must not be given to premature or newborn babies. It may cause toxic reactions and allergic reactions in infants and children up to 3 years old.

3. How Amiodarone will be given

Your doctor will decide on the correct dose to be given. This will depend upon your medical condition, age and bodyweight. The usual starting dose is 5mg/kg bodyweight, however this may vary depending on your age and how well you respond to treatment.

The solution is usually diluted before it is given to you. It will be given slowly, usually via an infusion (drip) into a vein in your arm or chest.

If too much or too little Amiodarone is given
As you will be given this product in a hospital or clinic where you will be closely monitored, it is unlikely that you will be given too little or too much, however tell your doctor or nurse if you have any concerns.

If you have any further questions on the use of this product, ask your doctor or nurse.

4. Possible side effects

Like all medicines, Amiodarone can cause side effects, although not everybody gets them.
Your doctor will monitor some side effects by blood tests (e.g. liver enzymes, thyroid function, anaemia and reduced clotting factors).

Tell your doctor or nurse immediately if you have any of the following:
Very rare side effects (in less than 1 in 10,000 people).
- Severe allergic reaction, recognised by an itchy rash, swelling of the face, lips, tongue or throat (which may cause difficulty in swallowing or breathing).
- Very slow heartbeat, which may stop particularly if you are elderly or have other heartbeat problems. You may also feel dizzy, tired and short of breath.
- Your heartbeat becomes more erratic or uneven. This may lead to a heart attack.
- Yellowing of the eyes or skin (jaundice), feeling tired or sick, loss of appetite, stomach pain or high temperature. These can be signs of serious liver damage.
- Difficulty or laboured breathing, tightness of the chest, dry cough, weight loss and fever. These may be signs of inflammation of the lungs.
- Headache, feeling sick, fits, confusion, fainting or eyesight problems. These may be signs of serious problems with your brain.

These are very serious side effects and you may need urgent medical attention.

Tell a doctor as soon as possible if you have any of the following:
Common side effects (in less than 1 in 10 people)
- Dizziness, light-headiness or fainting due to low blood pressure.

Tell your doctor or nurse if any of the following get serious or last more than a few days:
Common side effects (in less than 1 in 10 people)
- Slightly slower heart rate
- Reactions at the site of the injection such as pain, swelling, irritation or reddening of the skin.

Very rare side effects (in less than 1 in 10,000 people).
- Hot flushes, sweating
- Feeling sick
- Headache.

Other side effects (frequency unknown)
- Skin rash (hives).

If you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

5. How to store Amiodarone

Keep out of the reach and sight of children.
Do not store above 25°C. Keep ampoules in outer carton.
Do not use after the expiry date printed on the carton.

6. Further information

What Amiodarone 50mg/ml Sterile Concentrate contains
- Each ampoule contains 150mg of the active substance amiodarone hydrochloride.
- The other ingredients are polysorbate 80, benzyl alcohol and water for injections.

What this medicine looks like and contents of the pack
It is a clear, colourless or pale yellow solution, available as 3ml ampoules in packs of 5, 10 or 50 ampoules. Not all packs may be marketed.

Marketing Authorisation Holder
Beacon Pharmaceuticals Ltd, 85 High St., Tunbridge Wells, Kent TN1 1YG, UK
Manufacturer
Fisiopharma SRL, Palomonte 84020, Italy.

Date of last approval: MM/YYYY

Beacon PHARMACEUTICALS

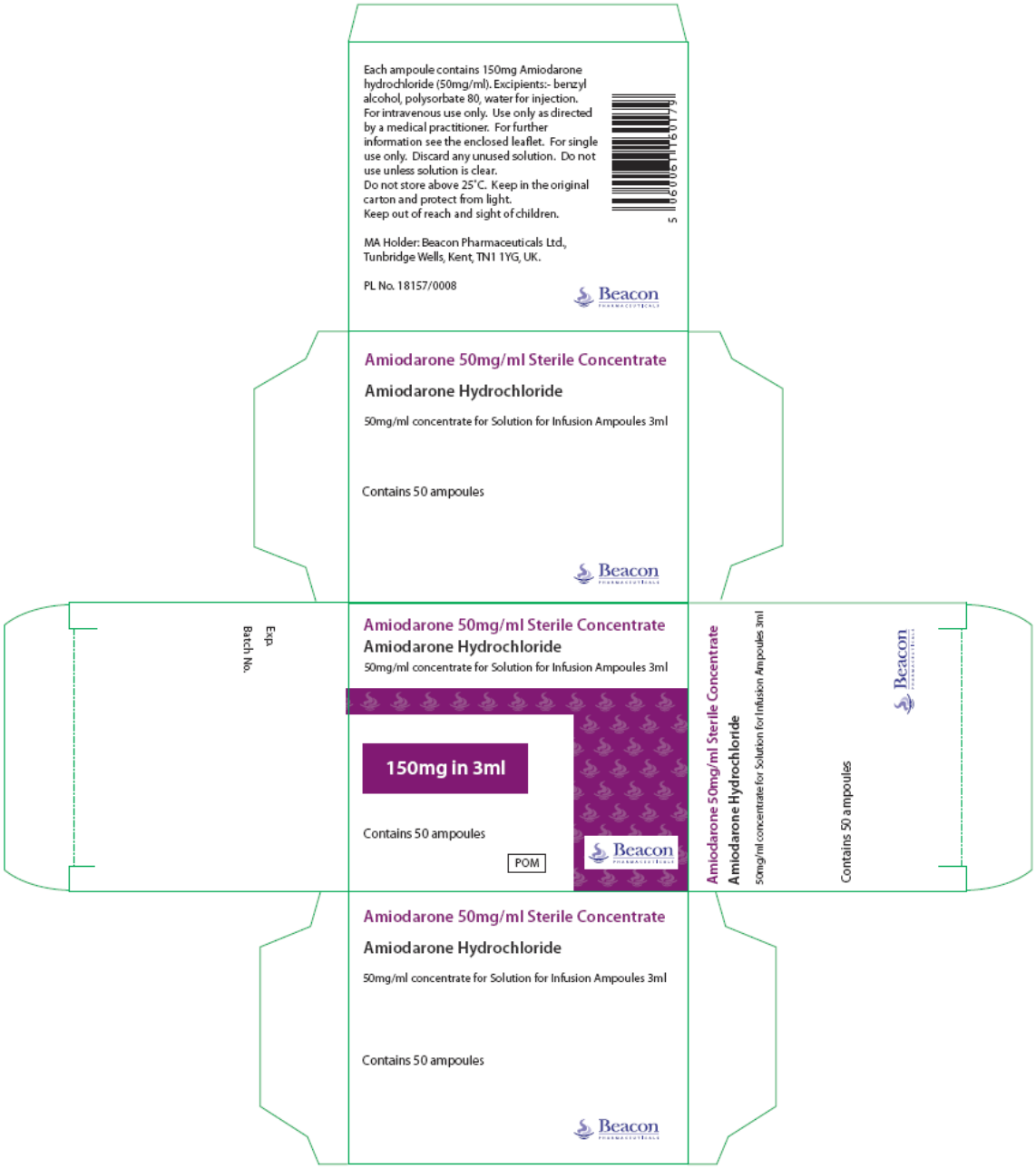
If needed, oral therapy may be initiated concomitantly. **Elderly**: There is no evidence that dosage requirements are different for this group of patients but they may be more susceptible to bradycardia and conduction defects if too high a dose is employed. Particular attention should be paid to monitoring thyroid function.
Cardiopulmonary resuscitation: The recommended dose for ventricular fibrillations/pulseless ventricular tachycardia resistant to defibrillation is 300 mg (or 5 mg/kg bodyweight) 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. **Pharmaceutical Information**. **Excipients**: Polysorbate 80, benzyl alcohol and Water for Injections. **Incompatibilities**: Amiodarone 50mg/ml Sterile Concentrate is incompatible with saline and should be administered solely in 5% Dextrose solution. Solutions containing less than 2 Amiodarone 50mg/ml ampoules 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. **Shelf-life**: 2 years **Storage Precautions**: Do not store above 25°C. Keep ampoules in the outer carton. **Nature of Container**: Type I glass ampoules in a plastic tray, in an outer carton. **Instructions for Use and Handling**: Please refer to Dosing instructions. For single use only. Discard any remaining solution.

LABELLING

Carton – pack size 5 ampoules

Carton – pack size 10 ampoules

Carton – pack size 50 ampoules



Ampoule label