## AMIODARONE HYDROCHLORIDE 50MG/ML
## STERILE CONCENTRATE

**PL 21523/0001**

**UKPAR**

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AMIODARONE HYDROCHLORIDE 50MG/ML STERILE CONCENTRATE

PL 21523/0001

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Amiodarone Hydrochloride 50mg/ml Sterile Concentrate (product licence number: 21523/0001).

Amiodarone Hydrochloride 50mg/ml Sterile Concentrate is a medicine used to control an irregular or rapid heart rate. Treatment should be initiated and monitored only under hospital or specialised supervision.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Amiodarone Hydrochloride 50mg/ml Sterile Concentrate outweigh the risks, hence a Marketing Authorisation has been granted.
AMIODARONE HYDROCHLORIDE 50MG/ML STERILE CONCENTRATE

PL 21523/0001

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Stragen France SAS a marketing authorisation for the medicinal product Amiodarone Hydrochloride 50mg/ml Sterile Concentrate (PL 21523/0001) on 7 August 2008. This medicine is available only on prescription.

Intravenous amiodarone hydrochloride 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, ventricular fibrillation) and atrial flutter and fibrillation. The injection is to be used when a rapid response is required. The proposed indications for this product are the same as for the brand leader.

This is a standard abridged application for Marketing Authorisation submitted under Article 10.1 of Directive 2001/83/EC for a concentrate for solution for infusion, containing 150mg amiodarone (as hydrochloride) in 3ml of solution (50mg/ml). The applicant claims that the proposed product is a generic version of the brand leader, Cordarone X Intravenous (PL 11723/0014), which is marketed in the UK by Sanofi Synthelabo. The brand leader product was first granted a Marketing Authorisation in the UK on 7 March 1983 and, hence, the 10-year period of data exclusivity has expired.

Amiodarone hydrochloride active ingredient is a well known substance which has been used for more than three decades for the treatment and prophylaxis of ventricular and paraventricular tachycardias in which other treatments have failed. The exact mechanism of the anti-arrhythmic action has not been conclusively determined, but the principal effect on cardiac tissue is to delay repolarisation by prolonging the action potential duration (APD) and effective refractory period (ERP). It also appears to inhibit transmembrane influx of extracellular sodium ions via fast sodium channels. Amiodarone also produces a non-competitive inhibition of alpha and beta-adrenergic activity that may contribute to its anti-arrhythmic activity. Limited data suggests the drug may posses some vagolytic and/or calcium-channel blocking activity. Amiodarone is considered to be predominantly a class III antiarrhythmic agent but it also appears to exhibit activity in each of the other classes.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

General information

Nomenclature

rINN: Amiodarone hydrochloride
Chemical names: (2-butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride
2-butyl-3-benzofuranyl-4-(2-diethylaminoethoxy)-3,5-di-iodophenyl ketone hydrochloride
CAS number: 19774-82-4

Structure

Molecular formula: C_{25}H_{29}I_{2}NO_{3}.HCl
Molecular weight: 681.8

General properties

A white or almost white, fine crystalline powder, freely soluble in chloroform, soluble in methanol, sparingly soluble in ethanol, very slightly soluble in water and hexane.

An appropriate specification based on the European Pharmacopoeia for amiodarone hydrochloride has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active amiodarone hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 5 years, when the drug substance is stored at temperatures not exceeding 25°C.
**DRUG PRODUCT**

**Other ingredients**
The drug product is presented as a sterile concentrate containing 150mg amiodarone hydrochloride. Other ingredients consist of pharmaceutical excipients, namely benzyl alcohol, polysorbate 80, water for injections, hydrochloric acid (pH adjustment) and sodium hydroxide (pH adjustment)

All excipients are controlled to their current Ph Eur specification and tested according to pharmacopoeial methodology. Representative Certificates of Analysis are presented.

It is confirmed that no materials of animal origin are employed, with all excipients obtained from synthetic or vegetable sources. A declaration to confirm this is presented from the supplier of polysorbate 80.

**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 has been carried out on product batches. The results are satisfactory.

**Finished product specification**
The finished product specification 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 working standards used.

**Container Closure System**
Three ml of the drug product is filled into colourless type I glass 5 ml ampoules. Each box contains 5 or 10 ampoules. Details provided of specifications applied and testing performed on the container are satisfactory.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, which is satisfactory. Storage conditions are “Do not store above 30°C” and “Store in the original packaging”.

Following dilution in 5% dextrose, chemical and physical in-use stability has been demonstrated for 36 hours at 25°C. From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

**Product literature**
All product literature (Summary of Product Characteristics, labelling and Patient Information Leaflet) is pharmaceutically satisfactory.
A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Bioavailability, bioequivalence**  
Given that this is an aqueous concentrate for a solution for intravenous administration, there is no requirement for a bioequivalence study.

**Generic status claim**  
This product contains the same amount of active ingredient as the brand leader. The product is qualitatively identical to the brand leader and is in the same pharmaceutical form. The impurity profile of the applicant’s product has been shown to be similar to that of the brand leader.

Therefore, the claim that this product is a generic version of the brand leader may be accepted.

**ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE**  
This application was of an overall high quality. The claim of essential similarity to the brand leader may be accepted.

A Marketing Authorisation should be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none is required for an application of this type.
CLINICAL ASSESSMENT

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

Amiodarone hydrochloride is indicated in:
- 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.

The injection is to be used where a rapid response is required or where oral administration is not possible.

DOSE & DOSE SCHEDULE
Amiodarone hydrochloride should only be used when facilities exist for cardiac monitoring, defibrillation, and cardiac pacing. Amiodarone hydrochloride 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.

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 hydrochloride must be closely monitored, e.g. in an intensive care unit.

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 hydrochloride 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. 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.

Cardiopulmonary 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.

TOXICOLOGY
The pharmacological and toxicological effects of amiodarone are well known. There is no reason to presume that there may be any unexpected toxicity from the use of the products in this application.

Efficacy
The efficacy profile of amiodarone hydrochloride is well established. No new efficacy data are required for these applications.

Safety
The safety profile of amiodarone is well established. No new efficacy data are required for theses applications.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

RECOMMENDATION
A product licence should be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Amiodarone Hydrochloride 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.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY AND SAFETY
The efficacy of amiodarone hydrochloride has been well documented in the past. No new or unexpected safety concerns arise from this application.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been demonstrated for Amiodarone Hydrochloride 50mg/ml Sterile Concentrate in the therapeutic indications proposed. The risk benefit is therefore considered to be positive.
**STEPS TAKEN FOR ASSESSMENT**

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<thead>
<tr>
<th>Step</th>
<th>Action</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 28 May 2004</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 1 July 2004</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information on the clinical and quality dossiers on 16 and 22 March 2005, respectively. The applicant responded to the MHRA’s requests, providing further information on 28 February 2007</td>
</tr>
<tr>
<td>4</td>
<td>The MHRA requested further information on the quality and clinical dossiers on 22 June and 9 August 2007, respectively. The applicant responded to the MHRA’s requests, providing further information on 12 October 2007.</td>
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<td>5</td>
<td>The MHRA requested further information on the quality dossier on 22 January 2008. The applicant responded to the MHRA’s requests, providing further information on 8 April 2008.</td>
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<tr>
<td>6</td>
<td>The MHRA requested further information on the quality dossier on 13 May 2008. The applicant responded to the MHRA’s requests, providing further information on 7 July 2008.</td>
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<tr>
<td>7</td>
<td>The MHRA requested further information on the quality dossier on 7 July 2008. The applicant responded to the MHRA’s requests, providing further information on 31 July 2008.</td>
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<tr>
<td>8</td>
<td>The application was determined on 7 August 2008.</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Amiodarone Hydrochloride 50mg/ml Sterile Concentrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 3ml ampoule contains 150mg Amiodarone hydrochloride. For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Concentrate for solution for injection of infusion (Sterile concentrate). The product is a clear, pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment should be initiated and normally monitored only under hospital or specialist supervision. Intravenous Amiodarone Hydrochloride is indicated only for the treatment of severe rhythm disorders not responding to other therapies or when other treatments cannot be used. Amiodarone hydrochloride is indicated in: 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 Hydrochloride can be used where a rapid response is required or where oral administration is not possible.

4.2 Posology and method of administration
Amiodarone Hydrochloride should only be used when facilities exist for cardiac monitoring, defibrillation, and cardiac pacing. Amiodarone Hydrochloride 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 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 Hydrochloride must be closely monitored, e.g. in an intensive care unit. (See 4.4 Special Warnings).

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 Hydrochloride 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 4.3 Contra-indications, 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 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 Contra-indications

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 Hydrochloride 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; congestive heart failure and cardiomyopathy are also contra-indications when using Amiodarone Hydrochloride as a bolus injection.

Known hypersensitivity to iodine or to amiodarone. (One ampoule contains approximately 56mg iodine).

The combination of Amiodarone Hydrochloride with drugs which may induce torsades de pointes is contra-indicated (see 4.5 Interactions).

Amiodarone Hydrochloride ampoules contain benzyl alcohol. There have been reports of fatal ‘gasp-ing syndrome’ in neonates (hypotension, bradycardia and cardiovascular collapse) following the administration of intravenous solution containing this preservative. Amiodarone Hydrochloride 150mg/3ml i.v. 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 4.6 Pregnancy)

Lactation (see 4.6 Lactation)
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 Hydrochloride 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 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).

Repeated or continuous infusion via peripheral veins may lead to local discomfort and inflammation. When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended. When given by infusion Amiodarone Hydrochloride may reduce drop size and, if appropriate, adjustments should be made to the rate of infusion.

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

**Cardiac disorders:**

Caution should be exercised in patients with hypotension and 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 proarhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic 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 Hydrochloride 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.

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 Hydrochloride 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 (see section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction).

### 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 Hydrochloride 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 4.3 Contra-indications) 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, fluphenazine, pimozone, haloperidol, amisulpiride and sertindole
- Lithium and tricyclic anti-depressants e.g. doxepin, maoi, 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, tetracosactrin, 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 amiodarone.

Drugs metabolised by cytochrome P450 3A4
When such drugs are co-administered with amiodarone, an inhibitor of CYP 3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity:
• 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**

None stated.

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 arrhythmia, sometimes followed by cardiac arrest (see sections 4.4 and 4.5).

**Blood and lymphatic system disorders:**

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

**Gastrointestinal disorders:**

- **Very rare:** nausea.

**General disorders and administration site conditions:**

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

**Hepato-biliary disorders:**

- **Very rare:**
  - Isolated increase in serum transaminases, which is usually moderate (1.5 to 3 times normal range) at the beginning of therapy. They may return to normal with dose reduction or even spontaneously.
  - acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, sometimes fatal (see section 4.4).

**Immune system disorders:**

- **Very rare:** anaphylactic shock.

**Nervous system disorders:**

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

**Respiratory, thoracic and mediastinal disorders:**

- **Very rare:**
  - interstitial pneumonitis (see section 4.4)
  - severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal (see sections 4.4 and 4.5)
- bronchospasm and/or apnoea in case of severe respiratory failure, and especially in asthmatic patients.

**Skin and subcutaneous tissue disorders:**
- Very rare: sweating.

**Vascular disorders:**
- Common: decrease in blood pressure, usually moderate and transient. Cases of hypotension or collapse have been reported following overdosage or a too rapid injection.
- Very rare: hot flushes.

### 4.9 Overdose

There is no information regarding overdose with intravenous Amiodarone hydrochloride. 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 group: antiarrhythmic (class III), ATC code: C01B D01. Amiodarone Hydrochloride 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 systemic/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
Hydrochloric acid (pH adjustment)
Sodium hydroxide (pH adjustment)

6.2 Incompatibilities
Amiodarone Hydrochloride is incompatible with saline. Solutions containing less than two ampoules of Amiodarone Hydrochloride 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
24 months
Following dilution in 5% dextrose, chemical and physical in-use stability has been demonstrated for 36 hours at 25°C.

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage
Do not store above 30°C.
Store in the original packaging

6.5 Nature and contents of container
Clear, type I glass ampoules containing 3 ml solution.
Each box contains 5 or 10 ampoules.

6.6 Special precautions for disposal
No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.
For single use only. Discard any unused solution.
The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to
administration. The solution should only be used if the solution is clear and free from particles. Amiodarone Hydrochloride should be administrated solely in 5% dextrose solution.
Amiodarone Hydrochloride must not be mixed with other medicinal products in the same syringe.
Intravenous infusion:
The calculated dose is diluted with 250 ml 5% dextrose. See section 4.2
Intravenous injection:
150-300 mg (corresponding to 3-6 ml Amiodarone Hydrochloride) is diluted with 10-20 ml 5% dextrose. See section 4.2

7 MARKETING AUTHORISATION HOLDER
Stragen France SAS
2 Rue de la Baleine
69005 Lyon
France

8 MARKETING AUTHORISATION NUMBER(S)
PL 21523/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/08/2008

10 DATE OF REVISION OF THE TEXT
07/08/2008
Amiodarone Hydrochloride 50 mg/ml is an anti-arrhythmic drug used to control an irregular or rapid heart rate. Treatment should be initiated and normally monitored only under hospital or specialist supervision.

1. WHAT AMIODARONE HYDROCHLORIDE 50 MG/ML STERILE CONCENTRATE IS AND WHAT IT IS USED FOR

Amiodarone Hydrochloride 50 mg/ml is an anti-arrhythmic drug used to control an irregular or rapid heart rate. Treatment should be initiated and normally monitored only under hospital or specialist supervision.

2. BEFORE AMIODARONE HYDROCHLORIDE 50 MG/ML STERILE CONCENTRATE IS GIVEN

Amiodarone Hydrochloride 50 mg/ml should not be given to you if:
- you have heart block which may cause a very slow, very fast or irregular pulse, or dizziness
- you have or have had thyroid problems
- you have severe respiratory failure or very low blood pressure
- it is being given as a single injection and you have low blood pressure, heart failure or cardiomyopathy (weakness of the heart muscle)
- you have an allergy to amiodarone, iodine or any of the other ingredients
- you are pregnant or likely to become pregnant. You should talk to your doctor regarding this
- you are breast-feeding
- you are taking other drugs including some other heart drugs (e.g. sotalol, anti-arrhythmics such as quinidine), monoamine oxidase inhibitors, antidepressants (including lithium), antihistamines, antimalarials, anti-infectives or stimulant laxatives.

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

Amiodarone Hydrochloride 50 mg/ml should be given 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)
- you are going to have an anaesthetic or high dose oxygen therapy
- you are anaemic.

Taking other medicines
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines - even those which your doctor has not prescribed for you, but which you have bought yourself from your chemist/pharmacy.

Before using Amiodarone Hydrochloride 50 mg/ml please check with your doctor if you are taking any of the following, in addition to the drugs listed in section 2. Before Amiodarone Hydrochloride 50 mg/ml is given, Amiodarone Hydrochloride 50 mg/ml should not be given to you if you are taking any of the following medicines:

- digoxin
- anti-coagulants - used to thin the blood (e.g. warfarin)
- phenytoin
- some calcium channel inhibitors - used to treat high blood pressure and angina (e.g. verapamil, diltiazem)
- heparin
- some antibiotics e.g. clindamycin
- beta blockers e.g. atenolol
- simvastatin or other statins (used to lower cholesterol levels)
- drugs which may change the levels of potassium or magnesium in your blood e.g. diuretics (water tablets), steriod tablets or the antifungal amphotericin

Taking Amiodarone Hydrochloride 50 mg/ml with food and drink
Grapefruit juice can increase the blood level of Amiodarone Hydrochloride 50 mg/ml and should be avoided during treatment with Amiodarone Hydrochloride 50 mg/ml.

Pregnancy and breast-feeding
Your doctor will prescribe Amiodarone Hydrochloride 50 mg/ml only if they consider the benefit of treatment outweighs the risks during your pregnancy. You should not be given Amiodarone Hydrochloride 50 mg/ml if you are breast-feeding.

Important information about some of the ingredients of Amiodarone Hydrochloride 50 mg/ml
Amiodarone Hydrochloride 50 mg/ml should only be given to premature babies and newborns (up to 1 month old) in exceptional circumstances. If your child is up to three years old, the benzyl alcohol in this product may cause unwanted reactions.

3. HOW AMIODARONE HYDROCHLORIDE 50 MG/ML IS GIVEN

Amiodarone Hydrochloride 50 mg/ml 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 Hydrochloride 50 mg/ml is 5 mg for every kg body weight given over 30 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 5 mg 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 dosage regimen may be considered only in exceptional circumstances and emergencies.

If you think that you may have been given too much Amiodarone Hydrochloride, please inform the doctor or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Amiodarone Hydrochloride 50 mg/ml can have side-effects. Common side-effects (reported by more than 1 in 10 people) are:

Heart and blood vessels
- a slow pulse
- a decrease in blood pressure
Skin
- local injection site reactions including swelling, pain, redness, infection and pigmentation changes

Other side-effects, which are very rare (reported in less than 1 in 100,000 people), are:

Heart and blood vessels
- chest pain or palpitations, or abnormal heart rhythm
- hot flushes

Digestive system
- nausea

Bones
- bone marrow granuloma (abnormal growth of cells in bone marrow)

Liver
- liver disorders including jaundice (yellowing of the eyes or skin)

Body as a whole (immune system)
- generalised allergic reactions such as swelling of the face, lips and/or tongue, shortness of breath, headaches

Respiratory system
- breathing difficulties (with or without fever), inability to breathe

Skin
- skin rash
- sweating

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

5. HOW TO STORE AMIODARONE HYDROCHLORIDE 50 MG/ML

Keep out of the reach and sight of children.

Do not store above 30°C.

Store in the original container in order to protect from light.

For single use only. Please discard any unused solution.

Do not use Amiodarone Hydrochloride 50 mg/ml after the expiry date which is stated on the ampoules and outer carton after EXP.

The expiry date refers to the last day of that month.

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

6. FURTHER INFORMATION

What Amiodarone Hydrochloride 50 mg/ml contains

The active substance is Amiodarone Hydrochloride. Each 3 ml ampoule contains 150 mg Amiodarone hydrochloride.

The other ingredients are Benzyl alcohol, Polysorbate 80 and Water for Injections.

What Amiodarone Hydrochloride 50 mg/ml looks like and contents of the pack

Amiodarone Hydrochloride 50 mg/ml is a clear solution.

It is supplied in boxes of 5 or 10 ampoules.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is:

STRAGEN France SAS
2 rue de la Balaine
69905 - LYON
FRANCE

The Manufacturer is:

FISIODPHARMA S.r.l.
NUCLEO INDUSTRIALE
84020 - PALOMONTE (SA)
ITALY

This leaflet was last approved in 08/2008

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THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY

Iodine content. One ampoule contains 50 mg iodine

For single use only.

Discard any unused solution.

The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Amiodarone should be administered in 5% dextrose solution only.

Amiodarone must not be mixed with other medicinal products in the same syringe.

Solutions containing less than 300 mg amiodarone (2 ampoules) in 500 ml of dextrose are not stable and must not be used. Do not mix any other compounds with amiodarone infusion solution.

The standard recommended dose is 5 mg/kg body weight given by intravenous infusion over a period of 20 minutes to 2 hours. This should be administered as a dilute solution in 250 ml 5% dextrose.

This may be followed by repeat infusion up to 1200 mg (approximately 15 mg/kg body weight) in up to 500 ml 5% dextrose per 24 hours, the rate of infusion being adjusted on the basis of clinical response.

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

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 (300 mg three times a day). Amiodarone Hydrochloride 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.

No controlled paediatric studies have been undertaken.

In published uncontrolled studies effective doses for children were:
- Loading dose: 5 mg/kg body weight over 20 minutes to 2 hours
- Maintenance dose: 10 to 15 mg/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.

Cardiopulmonary resuscitation

The recommended dose for ventricular fibrillation/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.
Use only as directed by a physician.

Read enclosed leaflet before use.

Keep out of the reach and sight of children.

Also contains: benzyl alcohol, Polysorbate 80 and water for injections

For single use only. Discard remainder after opening

Store in the original container in order to protect from light. Do not store above 30°C. Do not refrigerate.

For single use only. Discard remainder after opening.

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2 RUE DE LA BALEINE
69005 LYON
FRANCE

PL Number: 21523/0001

Each ampoule contains 150mg of amiodarone hydrochloride
Solution for intravenous infusion or slow injection

5 ampoules of 3 ml
Amiodarone hydrochloride 50 mg/ml
Concentrate for solution for infusion/injection

Amiodarone hydrochloride 50 mg/ml
Concentrate for solution for infusion/injection

Use only as directed by a physician.

Read enclosed leaflet before use.

Keep out of the reach and sight of children.

Also contains: benzyl alcohol, Polysorbate 80 and water for injections

For single use only. Discard remainder after opening

Store in the original container in order to protect from light.

Do not store above 30°C. Do not refrigerate.

For single use only. Discard remainder after opening.

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69006 LYON
FRANCE

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Amiodarone hydrochloride 50 mg/ml
Concentrate for solution for infusion/injection

Each ampoule contains 150mg of amiodarone hydrochloride

Solution for intravenous infusion or slow injection

10 ampoules of 3 ml