Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cordarone X Intravenous, 150mg/3ml, Concentrate for solution for infusion or slow injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 ml ampoule contains 150mg Amiodarone Hydrochloride (50mg/ml).

Excipients: contains benzyl alcohol 20mg/ml (60mg per 3ml ampoule).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for Solution for infusion or slow injection (sterile concentrate).
Colourless glass ampoule containing 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. Cordarone X Intravenous 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.

Atrial flutter and fibrillation when other drugs cannot be used.

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

Intravenous Cordarone can be used where a rapid response is required or where oral administration is not possible.

4.2 Posology and method of administration

Cordarone X Intravenous should only be used when facilities exist for cardiac monitoring, defibrillation and cardiac pacing.

Cordarone X Intravenous 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 infusions up to 1200mg, (approximately 15mg/kg bodyweight) in up to 500ml 5% dextrose per 24 hours, the rate of infusion being adjusted on the basis of clinical response. (*See Section 4.4*).

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

Cardiopulmonary resuscitation of shock resistant ventricular fibrillation: the recommended IV dose is 300mg (or 5mg/kg body weight) diluted in 20ml 5% dextrose and rapidly injected.
An additional 150mg (or 2.5mg/kg body weight) IV dose may be considered if ventricular fibrillation persists.

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 (i.e. 200mg three times a day). Cordarone X Intravenous should then be phased out gradually.

Paediatric patients
The safety and efficacy of Cordarone X Intravenous in children has not been established. Currently available data are described in sections 5.1 and 5.2.

Due to the presence of benzyl alcohol, Cordarone X Intravenous administration is contraindicated in newborns or premature neonates, infants and children up to 3 years old.

Elderly
As with all patients it is important that the minimum effective dose is used. Whilst there is no evidence that dosage requirements are different for this group of patients they may be more susceptible to bradycardia and conduction defects if too high a dose is employed. Particular attention should be paid to monitoring thyroid function. (*See Section 4.3, 4.4 and 4.8*). See section 6.2 for information on incompatibilities.

4.3 Contraindications

Sinus bradycardia, sinoatrial heart block and sick sinus syndrome. In patients with severe atrioventricular conduction disturbances (high grade AV block, bifascicular or trifascicular block), or sinus node disease Cordarone X should only be used in conjunction with a pacemaker.

Evidence or history of thyroid dysfunction *(see section 4.4)*.

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

The combination of Cordarone X with drugs which may induce torsades de pointes is contra-indicated (*see section 4.5)*.

Bi- or tri-fascicular conduction disorders, unless a permanent functioning pacemaker is fitted or, unless the patient is in a special care unit and amiodarone is used under the cover of electrosystolic pacing.

Severe arterial hypotension, circulatory collapse.

Intravenous injection is contra-indicated in case of hypotension, severe respiratory failure, myocardiopathy or heart failure (possible worsening).

Due to the presence of benzyl alcohol, which has been associated with reports of fatal 'gasping syndrome' in neonates, Cordarone X Intravenous is contraindicated in newborns or premature neonates, infants or young children up to 3 years old. (One ampoule contains 60mg of benzyl alcohol).

Pregnancy, except in exceptional circumstances (*see section 4.6*)

Lactation *(see section 4.6)*

In the case of cardiopulmonary resuscitation of shock resistant ventricular fibrillation where all other alternative therapies have failed, please consult section 4.2 and 4.4.1.

4.4 Special warnings and precautions for use

Specific to intravenous injection: see also contraindications 4.3

Intravenous injection is generally not advised because of haemodynamic effects sometimes associated with rapid injection (*see section 4.8*). Circulatory collapse may be precipitated by too rapid administration or overdosage (atropine has been used successfully in such patients presenting bradycardia).
Intravenous infusion is preferable whenever possible.

Intravenous injection should be performed only in an emergency where alternative therapies have failed and only in an intensive care unit under continuous monitoring (ECG, blood pressure).

Dosage is 5mg/kg body-weight
Except in cardiopulmonary resuscitation of shock resistant ventricular fibrillation, amiodarone should be injected over a minimum of 3 minutes, and intravenous injection should not be repeated less than 15 minutes following the first injection even if the latter was only 1 ampoule (possible irreversible collapse).

Do not mix other preparations in the same syringe. Do not inject other preparations in the same line. If amiodarone should be continued, this should be via intravenous infusion *(see section 4.2)*

Paediatric patients:
Cordarone X IV contains benzyl alcohol (20 mg/ml).
Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children up to 3 years old.

There have been reports of fatal 'gasping syndrome' in neonates (children less than one month of age) following the administration of intravenous solutions containing benzyl alcohol. Symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardiovascular collapse (see section 4.3).

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 proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects generally occur in the context of QT prolonging factors such as drug interactions and / or electrolytic disorders (*see sections 4.5. and 4.8*). Despite QT interval prolongation, amiodarone exhibits a low torsadogenic activity.

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, Cordarone X treatment should be withdrawn. If necessary beta-adrenostimulants or glucagon may be given. Because of the long half-life of amiodarone, if bradycardia is severe and symptomatic the insertion of a pacemaker should be considered.

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

Severe bradycardia and heart block
Life-threatening cases of bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone.

Bradycardia has generally occurred within hours to days, but later cases have been mostly observed up to 2 weeks after initiating HCV treatment.
Amiodarone should only be used in patients on sofosbuvir- containing regimen when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated.

Should concomitant use of amiodarone be considered necessary, it is recommended that patients undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Due to the long half-life of amiodarone, cardiac monitoring as outlined above should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofosbuvir- containing regimen.

All patients receiving amiodarone in combination with sofosbuvir-containing regimen should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

Pulmonary disorders:
Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity such as intertitial pneumonitis. 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 Cordarone X. 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)*.

Liver disorders *(see section 4.8):*
Close monitoring of liver function tests (transaminases) is recommended as soon as amiodarone is started and regularly during treatment. Acute liver disorders (including severe hepatocellular insufficiency or hepatic failure, sometimes fatal) and chronic liver disorders may occur with oral and intravenous forms within the first 24 hours of IV amiodarone. Therefore amiodarone dose should be reduced or the treatment discontinued if the transaminases increase exceeds three times the normal range. Clinical and biological signs of chronic liver disorders due to oral amiodarone may be minimal (hepatomegaly, transaminases, increased up to 5 times the normal range) and reversible after treatment withdrawal, however fatal cases have been reported.

Thyroid dysfunction:
Thyroid function tests should be performed where appropriate prior to therapy in all patients *(see section 4.3)*.

Hyperthyroidism may occur during amiodarone treatment or up to several months after discontinuation. Severe cases with clinical presentation of tyrotoxicosis, and sometimes fatal require emergency therapeutical management

Eye disorders (*see section 4.8*):
If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed. Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness. Unless blurred or decreased vision occurs, opthamological examination is recommended annually.

Severe bullous reactions:
Life threatening or even fatal cutaneous reactions Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (see section 4.8). If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present amiodarone treatment should be discontinued immediately.

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.

Caution should be exercised in case of hypotension, severe respiratory failure, uncompensated or severe heart failure *(also see section 4.3)*.

Cordarone X Intravenous should only be used in a special care unit under continuous monitoring (ECG and blood pressure).

To avoid injection site reactions *(see section 4.8), amiodarone IV should whenever possible be* administration by a central venous line.

When given by infusion Cordarone X 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 section 4.5*).

Primary Graft Dysfunction post cardiac transplant

In retrospective studies, amiodarone use in the transplant recipient prior to heart transplant has been associated with an increased risk of primary graft dysfunction (PGD).

PGD is a life-threatening complication of heart transplantation that presents as left, right or biventricular dysfunction occurring within the first 24 hours of transplant surgery for which there is no identifiable secondary cause (see Section 4.8). Severe PGD may be irreversible.

For patients who are on the heart transplant waiting list, consideration should be given to use an alternative antiarrhythmic drug as early as possible before transplant.

4.5 Interaction with other medicinal products and other forms of interactions

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

- Drugs inducing *Torsade de Pointes* or prolonging QT

- *Drugs inducing Torsade de Pointes*

Combined therapy with the following drugs that may induce '*torsade de pointes*' is contraindicated (see section 4.3)

- Class Ia anti-arrhythmic drugs such as quinidine, procainamide, disopyramide, bepridil
- Class III anti-arrhythmic drugs such as. sotalol, bretylium
- Non-antihythmic drugs such as: vincamine, some neuroleptic agents, cisapride, intravenous erythromycin, co-trimoxazole or pentamidine injection when parenterally administered), as there is an increased risk of potentially lethal "torsade de pointes",
- some anti-psychotics such as chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpiride and sertindole
- lithium and tricyclic anti-depressants such as doxepin, maprotiline, amitriptyline
- certain antihistamines such as terfenadine, astemizole, mizolastine
- anti-malarials such as quinine, mefloquine, chloroquine, halofantrine.

- *Drugs prolonging QT*

Co-administration of amiodarone with drugs known to prolong the QT interval must be based on a careful assessment of the potential risks and benefits for each patient since the risk of torsade de pointes may increase (see section 4.4) and patients should be monitored for QT prolongation.

Fluroquinolones should be avoided in patients receiving Amiodarone.

- Drugs lowering heart rate or causing automaticity or conduction disorders

Combined therapy with these drugs is not recommended:

Beta blockers and certain calcium channel inhibitors (diltiazem, verapamil); potentiation of negative chronotropic properties and conduction slowing effects may occur.

- Agents which may induce hypokalaemia:

Combined therapy with the following drugs is not recommended.

- stimulating laxative agents which may cause hypokalaemia thus increasing the risk of torsade de pointes.

Caution should be exercised when using the following drugs in combination with Cordarone:

- Diuretics inducing hypokalaemia, either alone or combined
- Systemic corticosteroids (gluco-, mineralo-), tetracosactide
- Amphotericin B (IV)

It is necessary to prevent the onset of hypokalaemia (and to correct hypokalaemia); the QT interval should be monitored and, in case of "*torsade de pointes*", anti-arrhythmic agents should not be given (ventricular pacing should be initiated; IV magnesium may be used).

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

- General Anesthesia (see section 4.4 and 4.8)

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, conduction disorder, decreased cardiac output.
Very rare cases of severe respiratory complications (adult acuterespiratory distress syndrome), sometimes fatal, have been observed usually in the period immediately following surgery. A possible interaction with a high oxygen concentration may be implicated.

EFFECT OF CORDARONE ON OTHER MEDICINAL PRODUCTS

Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP1A1, CYP1A2, CYP3A4, CYP2C9, CYP2D6, and P-glycoprotein and may increase exposure to their substrates.

Due to the long half life of amiodarone, interactions may be observed for several months after discontinuation of amiodarone.

- PgP substrates

Amiodarone is a P-gp inhibitor. Coadministration with P-gp substrates is expected to result in an increase in their exposure.

- *Digitalis*

Disturbances in automaticity (excessive bradycardia) and atrioventricular conduction (synergistic action) may occur; in addition, an increase in plasma digoxin concentrations is possible due to the decrease in digoxin clearance. ECG, and digoxin plasma levels should be monitored, and patients should be observed for clinical signs of digitalis toxicity. It may be necessary to adjust dosage of digitalis treatment.

- *Dabigatran*

Cautions should be exercised when amiodarone is co administered with dabigatran due to the risk of bleeding. It may be necessary to adjust the dosage of dabigatran as per its label.

- CYP 2C9 substrates

Amiodarone raises the concentrations of CYP 2C9 substrates such as warfarin or phenytoin by inhibition of the cytochrome P450 2C9.

- *Warfarin*

The combination of warfarin with amiodarone may exacerbate the effect of the oral anticoagulant thus increasing the risk of bleeding. It is necessary to monitor prothrombin (INR) levels more regularly and to adjust oral doses of anticoagulant agents both during treatment with amiodarone and after discontinuation of amiodarone treatment.

- *Phenytoin*

The combination of phenytoin with amiodarone may therefore lead to phenytoin overdosage, resulting in neurological signs. Clinical monitoring should be undertaken and phenytoin dosage should be reduced as soon as overdosage signs appear; phenytoin plasma levels should be determined.

- CYP 2D6 substrates

- *Flecainide*

Amiodarone raises plasma concentrations of flecainide by inhibition of CYP 2D6. Therefore the dosage of flecainide should be adjusted.

- CYP P450 3A4 substrates

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: combination with amiodarone may increase ciclosporin plasma levels. Dosage should be adjusted.
- Fentanyl: combination with amiodarone may enhance the pharmacologic effects of fentanyl and increase the risk of its toxicity.

- Statins: The risk of muscular toxicity (e.g rhabdomyolysis) is increased by concomitant administration of amiodarone with statins metabolized by CYP3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolized by CYP3A4 when given with amiodarone.
- Other drugs metabolised by CYP 3A4: lidocaine, sirolimus, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, colchicine.

EFFECTS OF OTHER DRUGS ON CORDARONE

CYP3A4 inhibitors and CYP2C8 inhibitors may have a potential to inhibit amiodarone metabolism and to increase its exposure.

It is recommended to avoid CYP3A4 inhibitors (e.g grapefruit juice and certain medicinal products) during treatment with amiodarone.

OTHER DRUG INTERACTIONS WITH AMIODARONE (see section 4.4)

Coadministration of amiodarone with sofosbuvir-containing regimens may lead to serious symptomatic bradycardia.

If coadministration cannot be avoided, cardiac monitoring is recommended (see section 4.4).

4.6 Fertility, pregnancy and lactation

In view of its effect on the foetal thyroid gland, amiodarone is contraindicated during pregnancy, except in exceptional circumstances.

Amiodarone is excreted in the breast milk in significant quantities and breast-feeding is contraindicated.

4.7 Effects on ability to drive and use machines

According to the safety data for amiodarone, there is no evidence that amiodarone impairs the ability to drive a vehicle, or operate machinery.

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%), unknown (cannot be estimated from available data).

Blood and lymphatic system disorders:

- Very rare

Haemolytic anemia, aplastic anaemia, thrombocytopenia.

- Not known

Neutropenia, agranulocytosis.

Cardiac disorders:

- Common

Bradycardia, generally moderate and dose-related.

- Uncommon

Onset or worsening of arrhythmia, sometimes followed by cardiac arrest *(see sections 4.4 and 4.5.)*, conduction disturbances (sinoatrial block, AV block of various degrees) (*see section 4.4*).

- Very rare

Marked bradycardia or sinus arrest in patients with sinus node dysfunction and / or in elderly patients.

- Not known

Torsade de pointes.

Endocrine disorders (*see section 4.4*):

- Common

Hypothyroidism, hyperthyroidism, sometimes fatal.

- Very rare

Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Eye disorders:

- Very common

Corneal microdeposits usually limited to the area under the pupil, which are usually only discernable by slit-lamp examinations. They may be associated with colored halos in dazzling light or blurred vision. Corneal micro-deposits consist of complex lipid deposits and are reversible following discontinuation of treatment. The deposits are considered essentially benign and do not require discontinuation of amiodarone.

- Very rare

Optic neuropathy / neuritis that may progress to blindness (*see section 4.4*).

Gastrointestinal disorders:

- Very common

Benign gastrointestinal disorders (nausea, vomiting, dysgeusia) usually occurring with loading dosage and resolving with dose reduction.

- Common

Constipation.

- Uncommon

Dry mouth.

- Not known

Pancreatitis/acute pancreatitis.

General disorders:

- Not known

Granuloma, including bone marrow granuloma.

Hepato-biliary disorders: (*see section 4.4*).

- Very common

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

- Common

Acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, which are sometimes fatal

- Very rare

Chronic liver disease (pseudo alcoholic hepatitis, cirrhosis), sometimes fatal.

Investigations:

- Very rare: increased serum creatinine.

Nervous system disorders:

- Common

Extrapyramidal tremor, for which regression usually occurs after reduction of dose or withdrawal, nightmares, sleep disorders.

- Uncommon

Peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the drug (*see section 4.4*).

- Very rare

Cerebellar ataxia, for which regression usually occurs after reduction of dose or withdrawal, benign intracranial hypertension (pseudo- tumor cerebri), headache, vertigo.

- Not known

Parkinsonism, parosmia.

Psychiatric disorders:

- Common

Libido decreased

- Not known

Confusional state/delirium, hallucination

Reproductive system and breast disorders:

- Very rare

Epididymo-orchitis, impotence.

Respiratory, thoracic and mediastinal disorders:

- Common

Pulmonary toxicity [hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia (BOOP)], sometimes fatal (*see section 4.4*).

- Not known

Pulmonary haemorrhage

- Very rare

Bronchospasm in patients with severe respiratory failure and especially in asthmatic patients, adult acute respiratory distress syndrome, sometimes fatal, most often immediately after surgery (possible interaction with a high oxygen concentration) (*see sections 4.4 and 4.5*).

Skin and subcutaneous tissue disorders:

- Very common:

Photosensitivity (*see section 4.4*)

- Common

Slate grey or bluish pigmentations of light-exposed skin, particularly the face, in case of prolonged treatment with high daily dosages; such pigmentations slowly disappear following treatment discontinuation. Eczema.

- Very rare

Erythema during the course of radiotherapy, skin rashes, usually non- specific, exfoliative dermatitis, alopecia.

- Not known:

Urticaria, severe skin reactions sometimes fatal including Toxic Epidermal Necrolysis /Stevens-Johnson syndrome, Bullous dermatitis and drug reactions with eosinophilia and systematic symptoms (DRESS).

Vascular disorders:

- Very rare

Vasculitis.

Immune system disorders:

- Not known

Angioneurotic edema (Quincke's oedema), anaphylactic/anaphylactoid reaction including shock.

Metabolism and nutrition disorders:

- Not known

Decreased appetite.

Musculoskeletal and Connective Tissue Disorders:

- Not known

Lupus like syndrome.

Injury, poisoning and procedural complications
- Frequency not known:
Primary graft dysfunction post cardiac transplant (see Section 4.4)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie

4.9 Overdose

There is no information regarding overdosage with intravenous amiodarone.

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

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

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

Neither amiodarone or its metabolites are dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C01BD01

Cordarone 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 on 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 safety and efficacy of amiodarone IV in patients with out-of hospital cardiac arrest due to shock resistant ventricular fibrillation have been evaluated in two double-blind studies: the ARREST study, a comparison of amiodarone to placebo, and the ALIVE study, a comparison of amiodarone to lidocaine.The primary endpoint of the both studies was survival to the hospital admission.

In the ARREST study, 504 patients with out-of hospital cardiac arrest resulting from ventricular fibrillation or pulseless ventricular tachycardia resistant to three or more defibrillation shocks and epinephrine, were randomised to amiodarone 300mg diluted in 20 ml 5 % dextrose rapidly injected into a peripheral vein (246 patients) or to placebo (258 patients). Of the 197 patients (39 %) who survived to be admitted to the hospital, amiodarone significantly increased the chances to be resuscitated and admitted to the hospital: 44 % in the amiodarone group and 34 % in the placebo group respectively, p = 0.03. After adjustment for other independent predictors of outcome, the adjusted odds ratio for survival to admission to the hospital in the amiodarone group as compared with the placebo group was 1.6 (95 % confidence interval, 1.1 to 2.4; p = 0.02). More patients in the amiodarone group than in the placebo group had hypotension (59 % versus 25 %, p = 0.04) or bradycardia (41% versus 25 %, p = 0.004).

In the ALIVE study, 347 patients with ventricular fibrillation resistant to three defibrillation shocks, epinephrine, and a further defibrillation shock, or with recurrence of ventricular fibrillation after initially successful debrillation, were randomised to receive amiodarone (5 mg per kilogram of estimated body-weight diluted in 30 ml 5 % dextrose) and lidocaine matching placebo, or lidocaine (1.5 mg per kilogram at a concentration of 10 mg per milliliter) and amiodarone matching placebo containing the same diluent (polysorbate 80). Of the 347 patients enrolled, amiodarone significantly increased the chances to be resuscitated and admitted to the hospital: 22.8 % in the amiodarone group (41 patients of 180) and 12 % in the lidocaine group (20 patients of 167), p = 0.009.

After adjustment for other factors that may influence the likelihood of survival, the adjusted odds ratio for survival to hospital admission in recipients of amiodarone as compared with recipients of lidocaine was 2.49 (95 percent confidence interval, 1.28 to 4.85; P=0.007). There were no differences between the treatment groups in the proportions of patients who needed treatment of bradycardia with atropine or pressor treatment with dopamine or in the proportions receiving open-label lidocaine. The proportion of patients in whom asystole occurred following defibrillation shock after administration of the initial study drug was significantly higher in the lidocaine group (28.9 %) than in the amiodarone group (18.4 %), p = 0.04.

No controlled paediatric studies have been undertaken.
In published studies the safety of amiodarone was evaluated in 1118 paediatric patients with various arrhythmias. The following doses were used in paediatric clinical trials.

Oral
- Loading dose: 10 to 20 mg/kg/day for 7 to 10 days (or 500 mg/m^2/day if expressed per square meter)
- Maintenance dose: the minimum effective dosage should be used; according to individual response, it may range between 5 to 10 mg/kg/day (or 250 mg/m^2/day if expressed per square meter)

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

If needed oral therapy may be initiated concomitantly at the usual loading dose.

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%).

Amiodarone is metabolized mainly by CYP3A4, and also by CYP2C8.
Amiodarone and its metabolite, desethylamiodarone, exhibit a potential *in vitro* to inhibit CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP2A6, CYP2B6 and 2C8. Amiodarone and desethylamiodarone have also a potential to inhibit some transporters such as P-gp and organic cation transporter (OCT2). (One study shows a 1.1% increase in concentration of creatinine (a OCT 2 substrate).
In vivo data describe amiodarone interactions on CYP3A4, CYP2C9, CYP2D6 and P-gp substrates.

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 approx 11 hours.

No controlled paediatric studies have been undertaken. In the limited published data available in paediatric patients, there were no differences noted compared to adults.

5.3 Preclinical safety data

In a 2-years carcinogenicity study in rats, amiodarone caused an increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinical relevant exposures. Since mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is proposed for this type of tumour induction. In the mouse, carcinomas were not observed, but a dose-dependent thyroid follicular hyperplasia was seen. These effects on the thyroid in rats and mice are most likely due to effects of amiodarone on the synthesis and/or release of thyroid gland hormones. The relevance of these findings to man is low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Polysorbate 80
Water for injections

6.2 Incompatibilities

Cordarone X Intravenous is incompatible with saline and should be administered solely in 5% dextrose solution. Solutions containing less than 2 ampoules Cordarone X intravenous in 500 ml dextrose 5% are unstable and should not be used. The use of administration equipment or devices containing plasticizers such as DeHP (Di-2-ethylhexylphalate) in the presence of amiodarone may result in leaching out of DeHP in order to minimise patients exposure to DeHP the final amiodarone dilution for infusion should preferably be administered through non DeHP containing sets.

6.3 Shelf life

Unopened: 2 years.
Once opened: Discard any unused protion immediately after opening.
Once diluted: Use immediately and discard any unused portion.

6.4 Special precautions for storage

Do not store above 25ºC.

Keep the ampoules in the outer carton.

6.5 Nature and contents of container

Clear, type I glass ampoules containing 3ml solution.

Pack sizes available, 6 glass ampoules and 10 glass ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Refer to Section 4.2 above.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/142/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 February 1984

Date of last renewal: 24 August 2007

10 DATE OF REVISION OF THE TEXT

March 2022