Safety Update CDS 12-15: original submission submitted 02.05.2013
BAU-resubmission: Response to 1st and 2nd CCR (rec 07.04.2016 and 27.06.2019) re-included + CCDS vs 16-21 + format change
Date submitted 12.01.2021 **To be implemented: 12.04.2021**

Proposed professional information (clean copy)

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

CORDARONE X® INTRAVENOUS (Concentrated solution for intravenous (IV) infusion/injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 3 ml ampoule contains 150 mg amiodarone hydrochloride (50 mg/ml)

organic iodine: approximately 56 mg

Excipient with a known effects: benzyl alcohol

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Clear, pale yellow concentrated solution for intravenous injection/infusion.

4 CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Where rapid response is required in the control of tachydysrhythmias associated with Wolff-Parkinson-White-syndrome and other types of tachydysrhythmias of paroxysmal nature including supraventricular, nodal and ventricular tachycardias, atrial flutter and atrial fibrillation and ventricular fibrillation which have proved to be resistant to other antidysrhythmic therapy.

Nadia Le Hanie *Regulatory Affairs Specialist*	

Cardiopulmonary resuscitation in the event of cardiac arrest in adults, caused by ventricular fibrillation resistant to external electric shock.

4.2 Posology and method of administration:

Posology:

Compatibility: Only 5 % dextrose should be used (see section 6.2).

General:

CORDARONE X INTRAVENOUS should only be used when facilities exist for cardiac monitoring or defibrillation, should the need arise (see section 4.4)

Intravenous infusion:

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

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

When given by infusion, CORDARONE X INTRAVENOUS may reduce drop size and, if appropriate, adjustments should be made to the rate of infusion.

Intravenous injection:

CORDARONE X INTRAVENOUS may, at the discretion of the clinician, be given as a bolus injection of 150 mg – 300 mg in 10 – 20 ml over a minimum of 3 minutes. This should not be repeated for at least 15 minutes. Patients treated in this way must be closely monitored, e.g. in an intensive care unit (see section 4.3).

Cardiopulmonary resuscitation of electro-shock resistant ventricular fibrillation:

In the specific case of cardio-pulmonary resuscitation of electro-shock resistant ventricular fibrillation, a first dose of 300 mg diluted in 20 ml of 5 % dextrose solution (or 5 mg/kg of estimated body weight diluted in 30 ml of 5 % dextrose).

CORDARONE X INTRAVENOUS is administered via bolus IV injection. An additional 150 mg (or 2,5 mg/kg) IV dose may be considered if the ventricular fibrillation persists.

Maintenance therapy:

Oral therapy should be initiated concomitantly at the usual loading dose as soon as possible after an adequate response is obtained and the intravenous therapy gradually phased out. 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.

Use in the elderly:

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.

4.3 Contraindications:

- Known hypersensitivity to iodine (one 3 ml ampoule contains approximately 56 mg iodine), to amiodarone or to any of the excipients of CORDARONE X INTRAVENOUS

- Sinus bradycardia, sinoatrial heart block and sick sinus syndrome (risk of sinus arrest), severe atrioventricular conduction disorders, unless a pacemaker is fitted
- Bifascicular or trifascicular disorders, unless a permanent pacemaker is fitted or, unless the patient is in a special care unit and CORDARONE X INTRAVENOUS is used under the cover of electrosystolic pacing
- Combined therapy with medicines which may induce Torsade de Pointes (see section 4.5)
- Severe respiratory failure, circulatory collapse and severe arterial hypotension
- Congestive heart failure when using CORDARONE X INTRAVENOUS as a bolus injection
- Intravenous injection in case of hypotension, myocardiopathy or heart failure (possible worsening)
- Prophylactic use in the preoperative period of cardio-pulmonary surgery
- Thyroid dysfunction (see section 4.4)
- Pregnancy (see section 4.6)
- Lactation (see section 4.6).

The above contraindications do not apply when CORDARONE X INTRAVENOUS is used in the emergency treatment of cardiopulmonary resuscitation of shock (defibrillator) resistant ventricular fibrillation.

Paediatric Patients: The safety and efficacy of CORDARONE X INTRAVENOUS in paediatric patients have not been established. Therefore, its use in paediatric patients is not recommended. The ampoules of CORDARONE X INTRAVENOUS contain benzyl alcohol (see section 4.4). 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 cardio-vascular collapse.

4.4 Special warnings and precautions for use:

Intravenous bolus injection is not advised because of haemodynamic risks (severe hypotension; circulatory collapse); intravenous infusion is preferable whenever possible. Intravenous bolus injection is to be done only in an emergency where alternative therapies have failed and only in a heart intensive care unit under continuous monitoring (ECG, blood pressure).

Dosage is approximately 5 mg/kg body-weight. Except for cases of cardiopulmonary resuscitation of electro-shock resistant ventricular fibrillation, CORDARONE X INTRAVENOUS should be injected over a minimum period of 3 minutes. Intravenous injection should not be repeated less than 15 minutes following the first injection even if the latter was only one ampoule (possible irreversible collapse).

Do not mix other preparations in the same syringe. Do not inject other preparations in the same line.

Where the treatment should be continued, continue with intravenous infusion (see section 4.2).

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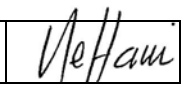
CORDARONE X INTRAVENOUS has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10-17 % in some series of patients with ventricular dysrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of some patients. Pulmonary toxicity has been fatal about 10 % of the time.

Liver injury is common with CORDARONE X INTRAVENOUS, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases.

CORDARONE X INTRAVENOUS can exacerbate the dysrhythmias e.g. by making the dysrhythmias less well-tolerated or more difficult to reverse. This has occurred in 2-5 % of patients in various series, and significant heart block or sinus bradycardia has been seen in 2-5 %.

Due to the long elimination half-life of CORDARONE X INTRAVENOUS**,** the risk of prodysrhythmic effects is prolonged after amiodarone is stopped.

Even in patients at high risk of dysrhythmic death, in whom the toxicity of CORDARONE X INTRAVENOUS is an acceptable risk, CORDARONE X INTRAVENOUS poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilise alternative medicines first.

Nadia Le Hanie *Regulatory Affairs Specialist*	

Please refer to detailed discussion under each point below.

CORDARONE X INTRAVENOUS should be avoided in patients with porphyria as it may precipitate an attack

Intravenous administration:

CORDARONE X INTRAVENOUS should only be used in a special care unit under continuous monitoring (ECG, blood pressure).

To avoid injection site reactions, CORDARONE X INTRAVENOUS should, whenever possible, be administrated through a central venous line.

Thyroid hormone abnormalities:

Both hyper- and hypothyroidism have occurred commonly during, or soon after, treatment with CORDARONE X INTRAVENOUS. Simple monitoring of the usual biochemical tests is confusing because some (PBI and ^{131}I uptake) are invalidated and others (T_4, T_3 and FTI) may be altered where the patient is clearly euthyroid. Clinical monitoring is therefore recommended and should be continued for some months after discontinuation of CORDARONE X INTRAVENOUS treatment. This is particularly important in the elderly. In patients whose history indicates an increased risk of thyroid dysfunction, regular testing is recommended.

Hyperthyroidism:

Clinical features of hyperthyroidism such as weight loss, asthenia, restlessness, increase in heart rate or a recurrence of the cardiac dysrhythmia, angina or congestive heart failure, should alert the clinician. The diagnosis may be supported by the finding of an elevated serum tri-

iodothyronine (T_3), a low level of thyroid stimulating hormone (TSH as measured by high sensitivity methods) and a reduced TSH response to thyrotrophin releasing hormone (TRH). Elevation of reverse T3(rT3) may also be found.

In the case of hyperthyroidism CORDARONE X INTRAVENOUS therapy should be withdrawn. Courses of anti-thyroid medication have been used for the treatment of severe thyroid hyperactivity; large doses may be required initially. These may not always be effective and concomitant high dose corticosteroid therapy may be required for several weeks.

Hypothyroidism:

The clinical features of hypothyroidism such as weight gain and reduced activity or excessive bradycardia should alert the clinician. The onset may be abrupt. The diagnosis may be supported by the presence of an elevated serum TSH level and an exaggerated TSH response to TRH. The thyroxine (T4), T3 and free thyroxine index (FTI) may be low.

Thyroid hypofunction usually resolves within 3 months of cessation of CORDARONE X INTRAVENOUS; it may be treated cautiously with L-thyroxine. Concomitant use of CORDARONE X INTRAVENOUS should only be used in life-threatening situations, when TSH levels may provide a guide to L-thyroxine dosage.

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 CORDARONE X INTRAVENOUS withdrawal due to the potential progression to blindness.

Cardiac disorders:

Onsets of new dysrhythmias or worsening of treated dysrhythmias, sometimes fatal, have been reported. It is important, but difficult, to differentiate a lack of efficacy of the medicine from a pro-dysrhythmic effect, whether or not this is associated with a worsening of the cardiac condition.

The pro-dysrhythmic effect of CORDARONE X INTRAVENOUS may occur alone or in combination with other QT prolonging factors, particularly other anti-dysrhythmic medicines, digoxin and hypokalaemia (see section 4.5). These effects are more rarely reported than with most of the other anti-dysrhythmic medicines and they generally occur in the case of certain medicine interactions or electrolytic disorders.

Despite QT interval prolongation, CORDARONE X INTRAVENOUS exhibits low torsadogenic activity (see section 4.5 and 4.8).

Latent or manifest heart failure may be worsened by CORDARONE X INTRAVENOUS**.** In this case, CORDARONE X INTRAVENOUS should be associated with the usual cardiotonic and diuretic treatments.

CORDARONE X INTRAVENOUS may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digoxin therapy. In these circumstances CORDARONE X INTRAVENOUS treatment should be withdrawn. If necessary, beta-adrenostimulants or glucagon may be given.

Cases of severe, potentially life-threatening bradycardia and heart block have been observed when CORDARONE X INTRAVENOUS is used in combination with sofosbuvir in combination with another hepatitis C virus (HCV) direct acting antiviral (DAA), such as daclatasvir, simeprevir, or ledipasvir. Therefore, coadministration of these medicines with CORDARONE X INTRAVENOUS is not recommended.

If concomitant use with CORDARONE X INTRAVENOUS cannot be avoided, it is recommended that patients are closely monitored when initiating sofosbuvir in combination with other DAAs. Patients who are identified as being at high risk of bradydysrhythmia should be continuously monitored for at least 48 hours in an appropriate clinical setting after initiation of the concomitant treatment with sofosbuvir.

Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued CORDARONE X INTRAVENOUS within the past few months and are to be initiated on sofosbuvir alone or in combination with other direct DAAs.

Patients receiving these hepatitis C medicines with CORDARONE X INTRAVENOUS, with or without other medicines that lower heart rate, should be warned of the symptoms of bradycardia and heart block and should be advised to seek urgent medical advice if they experience them.

Primary graft dysfunction (PGD) post cardiac transplant:

In retrospective studies, CORDARONE X INTRAVENOUS use in the transplant recipient prior to heart transplant has been associated with an increased risk of 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.

Pulmonary disorders:

Dyspnoea or non-productive cough, interstitial pneumonitis. Cases of interstitial pneumonitis have been reported with CORDARONE X INTRAVENOUS.

Imaging investigations should be performed when the diagnosis is suspected, in patients developing effort dyspnoea whether isolated, or, associated with deterioration of general health status (fatigue, weight loss, fever). CORDARONE X INTRAVENOUS therapy should be re-evaluated since interstitial pneumonitis may be reversible following early withdrawal of CORDARONE X INTRAVENOUS (clinical signs usually resolving within 3 to 4 weeks, followed by slower radiological and lung pulmonary function improvement within several months), and corticosteroid therapy should be considered.

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 section 4.5 and Anaesthesia).

Hepatic disorders:

Close monitoring of liver function tests (transaminases) is recommended as soon as CORDARONE X INTRAVENOUS 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 and within the first 24 hours of CORDARONE INTRAVENOUS. Therefore, the CORDARONE X INTRAVENOUS dose should be reduced or the treatment discontinued if the transaminases increase exceeds three times the normal range.

Patients with abnormal liver function tests should be reassessed clinically and tests of liver function should be monitored closely until they return to normal. If patients present with abnormal liver function tests, dosage reduction should be considered. If liver function test values continue to rise despite reduction in dosage (transaminases increase exceeds three times the normal range) or in situations where dosage reduction is not feasible, discontinuation of CORDARONE X INTRAVENOUS should be considered. The patient's clinical condition should be carefully monitored both as regards the hepatic condition and control of the dysrhythmias.

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 CORDARONE X INTRAVENOUS treatment should be discontinued immediately.

Concomitant use with other medicines:

Concomitant use of CORDARONE X INTRAVENOUS is not recommended with the following medicines: beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem), stimulating laxative agents which may cause hypokalaemia (see section 4.3 and 4.5

Anaesthesia:

Before surgery, the anaesthetist should be informed that the patient is taking CORDARONE X INTRAVENOUS (see section 4.5).

Benzyl alcohol:

CORDARONE X INTRAVENOUS contains 60 mg benzyl alcohol per 3 ml ampoule, which is equivalent to 20 mg/ml. Benzyl alcohol may cause allergic reactions (see section 2).[1]
Benzyl alcohol has been linked with the risk of severe side effects, including breathing problems called “gasping syndrome” in young children (see section 4.3).

High volumes should be used with caution and only if necessary, especially in patients with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interactions with other medicines and other forms of interaction:

PHARMACODYNAMIC INTERACTIONS:

Medicines inducing Torsade de Pointes or prolonging QT:

- **Medicines inducing Torsade de Pointes, which may be fatal:**

  The risk of Torsade de pointes may be increased when CORDARONE X INTRAVENOUS is used in combination with other medicines which directly or indirectly prolong the QT interval.

- **Combined therapy with medicines that may induce Torsade de Pointes is contraindicated** (see section 4.3), including:
  - Antidysrhythmic medicines such as Class Ia, sotalol, bepridil, disopyramide, quinidine.
  - Non-antidysrhythmic medicines such as vincamine, some neuroleptic medicines, cisapride, erythromycin IV, pentamidine (when administered parenterally)
  - Concomitant administration with dysrhythmogenic medicines for example phenothiazine antipsychotics,
  - Certain antihistamines such as mizolastine.
  - Antimalarials such as quinine, mefloquine, chloroquine, halofantrine.
  - Lithium and tricyclic antidepressants such as doxepin, maprotiline, amitriptyline.
- **Medicines prolonging QT:**

  Co-administration of CORDARONE X INTRAVENOUS with medicines 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 and patients should be monitored for QT prolongation.

  Fluoroquinolines should be avoided in patients receiving CORDARONE X INTRAVENOUS (e.g. moxifloxacin, ciprofloxacin).

Medicines lowering heart rate or causing automaticity or conduction disorders:

Combined therapy with the following medicines is not recommended:

Beta-blockers and heart rate lowering calcium channel inhibitors (verapamil, diltiazem) as automaticity (excessive bradycardia) and conduction disorders may occur.

Medicines which may induce hypokalaemia:

Combined therapy with the following medicines is not recommended:

Stimulating laxative medicines which may cause hypokalaemia such as senna and bisacodyl thus increasing the risk of Torsade de Pointes; other types of laxatives should be used.

Caution should be exercised when using the following medicines in combination with CORDARONE X INTRAVENOUS:

- Diuretics inducing hypokalaemia, either alone or combined
- Systemic corticosteroids (gluco-, mineralo-), **adrenocorticotrophic hormone (ACTH)**
- 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, antidysrhythmic medicines should not be given (ventricular pacing should be initiated; IV magnesium may be used).

General anaesthesia (see section 4.4)**:**

Potentially severe complications have been reported in patients receiving CORDARONE X INTRAVENOUS, undergoing general anaesthesia: bradycardia (unresponsive to atropine), hypotension, disturbances of conduction, decreased cardiac output.

Cases of severe respiratory complications (adult acute respiratory 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 X INTRAVENOUS ON OTHER MEDICINAL PRODUCTS:

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

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

- **PgP substrates:** Amiodarone is a P-gp inhibitor. Co-administration with P-gp substrates is expected to result in an increase of their exposure.
  - ***Digoxin:*** The plasma concentrations of digoxin may be raised with the concomitant administration of CORDARONE X INTRAVENOUS. Administration of CORDARONE X INTRAVENOUS to a patient already receiving digoxin may bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels. Monitoring of ECG and plasma levels is recommended and digoxin dosage should be adjusted accordingly. A synergistic effect on heart rate and atrioventricular conduction is also possible
  - ***Dabigatran*:** Caution should be exercised when CORDARONE X INTRAVENOUS is co-administered with dabigatran due to the risk of bleeding. It may be necessary to adjust the dosage of dabigatran as per its package insert.
- **CYP2C9 substrates:** CORDARONE X INTRAVENOUS raises the concentrations of CYP2C9 substrates such as warfarin or phenytoin by inhibition of the cytochrome P450 2C9
  - ***Warfarin:*** CORDARONE X INTRAVENOUS raises the concentration of warfarin by inhibition of the cytochrome P450 2C9. The combination of warfarin with CORDARONE X INTRAVENOUS may exacerbate the effect of the warfarin thus increasing the risk of bleeding. It is necessary to monitor prothrombin (INR) levels more regularly and to adjust

oral doses of warfarin both during treatment with CORDARONE X INTRAVENOUS and after discontinuation of CORDARONE X INTRAVENOUS treatment

- **Phenytoin:** Consideration should be given to the possibility that CORDARONE X INTRAVENOUS may alter the plasma concentrations of other medicines, particularly those which are highly protein-bound e.g. phenytoin.

  The combination of phenytoin and CORDARONE X INTRAVENOUS may lead to phenytoin overdosage, resulting in neurological signs. Clinical monitoring should be undertaken and phenytoin dosage should be reduced if overdosage signs appear; phenytoin plasma levels may be determined when necessary.

  In addition, plasma CORDARONE X INTRAVENOUS concentrations may be decreased by phenytoin.

- **CYP2D6 substrates:**
  - **Flecainide:** CORDARONE X INTRAVENOUS raises plasma concentrations of flecainide by inhibition of the cytochrome CYP2D6. Therefore, flecainide dosage should be adjusted accordingly and the patient closely monitored
- **CYP P450 3A4 substrates:** When such medicines are co-administered with CORDARONE X INTRAVENOUS, an inhibitor of CYP3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity:
  - **Ciclosporin**: its combination with CORDARONE X may increase ciclosporin plasma levels. Dosage should be adjusted
  - **Fentanyl**: its combination with CORDARONE X INTRAVENOUS 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 CORDARONE X INTRAVENOUS with statins especially those

metabolised by CYP3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended not to use a statin combined with CORDARONE X INTRAVENOUS

- **Other medicines metabolised by CYP3A4**: lidocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, colchicine.

- **Others:**

  The effects of clonazepam may be enhanced by concomitant administration of CORDARONE X INTRAVENOUS, and plasma concentrations of procainamide, and quinidine may be raised.

EFFECT OF OTHER MEDICINES ON CORDARONE X INTRAVENOUS:

CYP3A4 inhibitors and CYP2C8 inhibitors may have a potential to inhibit CORDARONE X INTRAVENOUS metabolism and to increase its exposure.

It is recommended to avoid CYP3A4 inhibitors (e.g. grapefruit juice and certain medicines during treatment with CORDARONE X INTRAVENOUS.

Plasma CORDARONE X INTRAVENOUS concentrations may be increased by cimetidine and other inhibitors of metabolising enzymes CYP3A4 including HIV-protease inhibitors.

Coadministration of CORDARONE X INTRAVENOUS with sofosbuvir alone or in combination with another HCV direct acting antiviral (such as daclatasvir, simeprevir, or ledipasvir) is not recommended as it may lead to serious symptomatic bradycardia. The mechanism for this bradycardia effect is unknown. If coadministration cannot be avoided, cardiac monitoring is recommended (see section 4.4).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

In view of amiodarone's effect on the foetal thyroid gland, CORDARONE X INTRAVENOUS is contraindicated during pregnancy.

Breastfeeding:

CORDARONE X INTRAVENOUS is excreted into the breastmilk in significant quantities and breastfeeding is contraindicated (see section 4.3).

4.7 Effects on the ability to drive and use machines:

Driving or operating machinery should be carried out with caution because CORDARONE X INTRAVENOUS causes blurred vision and coloured halos in dazzling light.

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).

Immune system disorders:

Very rare: anaphylactic shock

Blood and lymphatic system disorders:

Very rare: haemolytic anaemia, aplastic anaemia and thrombocytopenia

Endocrine disorders:

Common: hypothyroidism and hyperthyroidism, sometimes fatal

Very rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Nervous system disorders:

Very rare: benign intracranial hypertension, nightmare, headaches, vertigo and sleeplessness

Cardiac disorders:

Common: bradycardia, generally dose-related. ECG changes, i.e. QT interval lengthening corresponding to prolonged repolarisation; U-waves and deformed T-waves may occur

Uncommon: conduction disturbances (sinoatrial block, AV block of various degrees)

Very rare: marked bradycardia or sinus arrest in patients with sinus node dysfunction and/or in elderly patients. Onset of new dysrhythmia or worsening of existing dysrhythmia, sometimes followed cardiac arrest (see section 4.4)

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 (see section 4.2)

Very rare: temporary hot flushes

Gastrointestinal disorders:

Very rare: nausea, vomiting and metallic taste

General disorders and administration site conditions:

Common: local inflammation of veins following intravenous infusion may be avoided by the use of a central venous catheter. 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 increases 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. Acute liver disorders with high serum transaminases and/or cholestasis with jaundice including hepatic failure, sometimes fatal (see section 4.4)

Post-marketing data:

Blood and lymphatic system disorders: neutropenia, agranulocytosis

Immune system disorders: angioedema (Quincke's Oedema)

Psychiatric disorders: confusional state/delirium, hallucination

Eye disorders: optic neuropathy/neuritis that may progress to blindness

Cardiac disorders: Torsade de Pointes (see section 4.4 and 4.5)

Gastrointestinal disorders: pancreatitis/ acute pancreatitis

Skin and subcutaneous tissue disorders: urticaria, eczema, severe skin reactions sometimes fatal including Toxic Epidermal Necrolysis (TEN)/Stevens- Johnson syndrome (SJS), bullous dermatitis, Drug reaction with Eosinophilia and Systematic Symptoms (DRESS)[16] (see section 4.4).

Musculoskeletal and connective tissue disorders:

back pain

Reproductive system and breast disorders: libido decreased

Injury, poisoning and procedural complications: primary graft dysfunction post cardiac transplant (section 4.4)

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: Email: za.drugsafety@sanofi.com or Tel: 011 256-3700, or

SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Overdosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in the elderly patients or during digoxin therapy. In these circumstances, CORDARONE X INTRAVENOUS treatment should be withdrawn.
In the event of an overdosage general supportive measures should be employed. The patient should be monitored and if bradycardia ensues beta-adrenostimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of CORDARONE X INTRAVENOUS, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended.

5. PHARMACOLOGICAL PROPERTIES:

A 6.2 Cardiac depressants.

Pharmacotherapeutic group: Cardiac therapy, antiarrhythmics, class III. ATC code: C01BD01.

5.1 Pharmacodynamic properties:

Electrophysiological studies demonstrated that amiodarone prolongs the duration of the action potential, particularly in the nodal and Purkinje tissue. Amiodarone does not appear to alter the resting membrane potential, but depresses membrane responsiveness, and prolongs the refractory period in the atria, AV node, His-Purkinje System, ventricles and accessory atrioventricular conduction pathways. The conduction rate is reduced in the atria, AV node and accessory pathways. Amiodarone also demonstrates non-competitive alpha and beta adrenoreceptor antagonism.

5.2 Pharmacokinetic properties:

The average bioavailability of amiodarone after oral administration is about 50 %, but varies widely . It is extensively distributed to body tissues and accumulates in fat as well as in skeletal muscles and highly perfused tissues such as liver, lungs, and spleen. Amiodarone has been reported to be about 96 % bound to plasma proteins.

The terminal elimination half-life is about 50 days with a range of about 20 to 100 days due to its extensive tissue distribution. On stopping prolonged amiodarone therapy a pharmacological effect is evident for more than a month. A major metabolite, desethylamiodarone, has antidysrhythmic properties.

There is very little urinary excretion of amiodarone or its metabolites, the major route of excretion being faeces via the bile; some enterohepatic recycling may occur.

Amiodarone and desethylamiodarone are reported to cross the placenta and to be distributed into breast milk.

Amiodarone is metabolised 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.

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 is considered to be low.

6 PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Benzyl alcohol (see section 4.4)

Polysorbate 80

Water for injection

Nitrogen (head space gas)

6.2 Incompatibilities:

CORDARONE X INTRAVENOUS is incompatible with saline and should be administered solely in 5 % dextrose.

Solutions containing less than 2 ampoules CORDARONE X INTRAVENOUS in 500 ml of 5 % dextrose are unstable and should not be used.

The use of medical equipment or devices containing plasticiser such as DEHP (di-2-ethylhexyl phthalate) in the presence of CORDARONE X INTRAVENOUS result in leaching out of DEHP. In order to minimise patient exposure to DEHP, the final CORDARONE X INTRAVENOUS dilution for infusion may preferably be administered through non DEHP-containing sets.

Do not mix with other preparations in the same syringe.

6.3 Shelf life:

24 months

6.4 Special precautions for storage

Protect from light and store in a cool place at or below 25 ºC. Keep the ampoule in the carton until required for use.

6.5 Nature and contents of container:

5 ml clear and colourless glass ampoules containing 3 ml solution for intravenous injection/infusion, packed in units of 6 on a tray with a leaflet in a carboard carton.

6.6 Special precautions for disposal and other handling

Compatibility: Only 5 % dextrose should be used for dilution (See section 4.2). Solutions containing less than 2 ampoules CORDARONE X INTRAVENOUS in 500 ml of 5 % dextrose are unstable and should not be used (see section and 6.2).

7 HOLDER OF CERTIFICATE OF REGISTRATION:

sanofi-aventis south africa (pty) ltd.

2 Bond Street

Midrand, 1685

South Africa

8 REGISTRATION NUMBER[~~S~~]:

S/6.2/384

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

11 November 1987

10 DATE OF REVISION OF THE TEXT:

To be allocated

NAMIBIA:

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Nadia Le Hanie *Regulatory Affairs Specialist*