Cordarone

Amiodarone Hydrochloride 150mg/3ml

Solution for injection in ampoules

[sanofi logo]

Composition:
Each 3ml ampoule contains 150mg amiodarone hydrochloride.

Pharmaceutical Form
Solution for injection.

Clinical Particulars
Therapeutic Indications
Treatment should be initiated and normally monitored only under hospital or specialist supervision. Cordarone 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.
All types of tachyarrhythmias including supraventricular, nodal and ventricular tachycardias; atrial flutter and fibrillation; ventricular fibrillation; when other drugs cannot be used.
Cordarone Intravenous can be used where a rapid response is required or where oral administration is not possible.
Cardiopulmonary resuscitation in the event of cardiac arrest related to ventricular fibrillation resistant to external electric shock.

Posology and Method of Administration
Cordarone Intravenous should only be used when facilities exist for cardiac monitoring, defibrillation, and cardiac pacing.
Cordarone 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 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 Special Warnings and Special Precautions for Use).*
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 Intravenous must be closely monitored, e.g. in an intensive care unit. *(see Special Warnings and Special Precautions for Use).*

Change over 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 Intravenous should then be phased out gradually.

Pediatric population
The safety and efficacy of amiodarone in children has not been established.
Due to the presence of benzyl alcohol, intravenous amiodarone is usually contraindicated in neonates and premature babies *(see Contraindications).*

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 Contraindications, Special Warnings and Special Precautions for Use and Undesirable Effects).*

Cardiopulmonary resuscitation
The recommended dose for ventricular fibrillations/pulseless ventricular tachycardia resistant to defibrillation is 300 mg (or 5 mg/kg bodyweight) diluted in 20 ml 5% dextrose and rapidly injected. An additional 150 mg (or 2.5 mg/kg bodyweight) IV dose may be considered if ventricular fibrillation persists.
See Incompatibilities for information on incompatibilities

Contraindications
Sinus bradycardia and sino-atrial heart block. In patients with severe conduction disturbances (high grade AV block, bifascicular or trifascicular block) or sinus node disease, Cordarone should be used only in conjunction with a pacemaker.
Evidence or history of thyroid dysfunction. Thyroid function tests should be performed where appropriate prior to therapy in all patients.
Severe respiratory failure, circulatory collapse, or severe arterial hypotension; hypotension, heart failure and cardiomyopathy are also contraindications when using Cordarone Intravenous as a bolus injection.
Known hypersensitivity to iodine or to amiodarone, or to any of the excipients. (One ampoule contains approximately 56mg iodine).
The combination of Cordarone with drugs which may induce torsades de pointes is contraindicated *(see Interactions with Other Medicinal Products and Other Forms of Interaction).*
Cordarone Intravenous ampoules contain benzyl alcohol. There have been reports of fatal 'gasping syndrome' in neonates (hypotension, bradycardia and cardiovascular collapse) following the administration of intravenous solution containing this preservative. Cordarone Intravenous 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 Pregnancy and Lactation).*
Lactation *(see Pregnancy and Lactation)*
All these above contraindications do not apply to the use of amiodarone for cardiopulmonary resuscitation of shock resistant ventricular fibrillation.

Special Warnings and Special Precautions for Use
Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children up to 3 years old.
Cordarone Intravenous 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 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 injection site reactions *(see Undesirable Effects).* When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended.
When given by infusion Cordarone may reduce drop size and, if appropriate, adjustments should be made to the rate of infusion.
Anaesthesia *(see Interactions with Other Medicinal Products and Other Forms of Interaction):* Before surgery, the anaesthetist should be informed that the patient is taking amiodarone.

Cardiac disorders (see *Undesirable Effects*)
Caution should be exercised in patients with hypotension and decompensated cardiomyopathy and severe heart failure *(also see Contraindications).*
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 Interactions with Other Medicinal Products and Other Forms of Interaction and Undesirable Effects)*. 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 treatment should be withdrawn. If necessary betaadrenostimulants 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.

Before starting amiodarone, it is recommended to perform an ECG and serum potassium measurement. Monitoring of ECG is recommended during treatment.
Amiodarone may increase the defibrillation threshold and/or pacing threshold in patients with an implantable cardioverter defibrillator or a pacemaker, which may adversely affect the efficacy of the device. Regular tests are recommended to ensure the proper function of the device after initiation of treatment or change posology.

Severe Bradycardia (see *Undesirable Effects*) :
Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone is used in combination with sofosbuvir alone or in combination with another hepatitis C virus (HCV) direct acting antiviral (DAA), such as daclatasvir, simeprevir, or ledipasvir. Therefore, coadministration of these agents with amiodarone is not recommended.
If concomitant use with amiodarone cannot be avoided, it is recommended that patients are closely monitored when initiating sofosbuvir alone or in combination with other DAAs.
Patients who are identified as being at high risk of bradyarrhythmia 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 amiodarone 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 amiodarone, 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.

Transplantation
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 Undesirable effects). 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.

Endocrine disorders (see section *Undesirable Effects*)
Amiodarone IV may induce hyperthyroidism, particularly in patients with a personal history of thyroid disorders or patients who are taking/have previously taken oral amiodarone. Serum usTSH level should be measured when thyroid dysfunction is suspected.
Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T3, free-T4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of levothyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum free-T4, free-T3 being slightly decreased or even normal) in clinically euthyroid patients. There is no reason in such cases to discontinue amiodarone treatment if there is no clinical or further biological (usTSH) evidence of thyroid disease.

Eye disorders
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.

Respiratory, thoracic and mediastinal disorders (see Undesirable Effects)
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 Undesirable Effects).* Clinical symptoms often resolve within a few weeks followed by slower radiological and lung function improvement. Some patients can deteriorate despite discontinuing Cordarone.
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 Interactions with Other Medicinal Products and Other Forms of Interaction and Undesirable Effects).*

Hepato-biliary disorders (see Undesirable Effects)
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.

Severe bullous reactions
Life-threatening or even fatal cutaneous reactions Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (see Undesirable Effects). 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 Interactions with Other Medicinal Products and Other Forms of Interaction)
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.

Interactions 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 CYP 2C9 substrates such as 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 Cordarone 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 contraindicated *(see Contraindications)* due to the increased risk of torsades de pointes; for example:
- Class Ia anti-arrhythmic drugs e.g. quinidine, procainamide, disopyramide
- Class III anti-arrhythmic drugs e.g. sotalol, bretylium
- intravenous erythromycin, co-trimoxazole or pentamidine injection
- some anti-psychotics e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride and sertindole
- lithium and tricyclic anti-depressants e.g. doxepin, maprotiline, amitriptyline

- certain antihistamines e.g. terfenadine, astemizole, mizolastine
- anti-malarials e.g. quinine, mefloquine, chloroquine, halofantrine.
- moxifloxacin
- drugs lowering heart rate or causing automaticity or conduction disorders

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 Special Warnings and Special Precautions for Use*) and patients should be monitored for QT prolongation.

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 contraindicated, see above).

Combined therapy with the following drugs is not recommended:
• Beta blockers and certain calcium channel inhibitors (diltiazem, verapamil); potentiation of negative chronotropic properties and conduction slowing effects may occur.
• Stimulant laxatives, which may cause hypokalaemia thus increasing the risk of torsades de pointes; other types of laxatives should be used.
Caution should be exercised over combined therapy with the following drugs which may also cause hypokalaemia and/or hypomagnesaemia: e.g. diuretics, systemic corticosteroids, tetracosactide, intravenous amphotericin.
In cases of hypokalaemia, corrective action should be taken and QT interval monitored. In case of torsades de pointes antiarrhythmic agents should not be given; pacing may be instituted and IV magnesium may be used.
Caution is advised in patients undergoing general anaesthesia, or receiving high dose oxygen therapy. Potentially severe complications have been reported in patients taking amiodarone undergoing general anaesthesia: bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output. A few cases of adult respiratory distress syndrome, most often in the period immediately after surgery, have been observed. A possible interaction with a high oxygen concentration may be implicated.
Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP 1A1, CYP 1A2, CYP 3A4, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2A6, CYP 2B6, CYP 2D6, P-glycoprotein and organic cation transporter 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 amiodarone.
Amiodarone is a strong P-gp inhibitor. Co-administration with P-gp substrates is expected to result in an increase of their exposure.
Caution 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.

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:
• Cyclosporin: plasma levels of cyclosporin may increase as much as 2-fold when used in combination. A reduction in the dose of cyclosporin may be necessary to maintain the plasma concentration within the therapeutic range.
• Statins: the risk of muscular toxicity is increased by concomitant administration of amiodarone with statins metabolized by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolized by CYP 3A4 when given with amiodarone.
• Other drugs metabolised by cytochrome P450 3A4: examples of such drugs are the lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine, ergotamine and colchicine.

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.

CYP 3A4 and CYP 2C8 inhibitors may have a potential to inhibit amiodarone metabolism and to increase its exposure. It is recommended to avoid CYP 3A4 inhibitors (e.g. grapefruit juice and certain medicinal products) during treatment with amiodarone.

HCV direct acting antiviral
Coadministration of amiodarone 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.

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 breastfeeding is contraindicated.

Effects on Ability to Drive and Use Machines
Not relevant.

Undesirable Effects
The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention: very common (> = 10%), common (> = 1% and < 10%); uncommon (> = 0.1% and < 1%); rare (> = 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from available data).

Blood and lymphatic system disorders:
- Frequency not Known: In patients taking amiodarone there have been incidental findings of bone marrow granulomas. Neutropenia, agranulocytosis.

Cardiac disorders:
- Common: bradycardia, generally moderate
- Very rare:

- marked bradycardia, sinus arrest requiring discontinuation of amiodarone, especially in patients with sinus node dysfunction and/or in elderly patients
- onset of worsening of arrythmia, sometimes followed by cardiac arrest *(see Special Warnings and Special Precautions for Use and Interactions with Other Medicinal Products and Other Forms of Interaction)*

- Frequency not known:

- Torsades de points (*see Special Warnings and Special Precautions for Use and Interactions with Other Medicinal Products and Other Forms of Interaction*)

Endocrine disorders:
• Common: hypothyroidism
• Frequency not known: hyperthyroidism (see *Special warnings and precautions for use*)
• Very rare: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Eye disorders
• Frequency not known: Optic neuropathy/neuritis that may progress to blindness

Gastrointestinal disorders:
• Very rare: nausea,
• Frequency Not known: pancreatitis/ acute pancreatitis

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 Special Warnings and Special Precautions for Use)*

Immune system disorders:
• Very rare: anaphylactic shock
• Frequency not known: angioedema, anaphylactic/anaphylactoid reaction including shock.

Musculoskeletal and connective tissue disorders
• Frequency not known: back pain

Nervous system disorders:
• Very rare: benign intra-cranial hypertension (pseudo tumor cerebri), headache

Psychiatric disorders:
• Frequency not known: Confusional state/delirium, hallucination

Reproductive system and breast disorders
• Frequency not known: Libido decreased

Respiratory, thoracic and mediastinal disorders:
• Very rare:
- interstitial pneumonitis or fibrosis, sometimes fatal *(see Special Warnings and Special Precautions for Use)*
- severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal *(see Special Warnings and Special Precautions for Use and Interactions with Other Medicinal Products and Other Forms of Interaction)*
- bronchospasm and/or apnoea in case of severe respiratory failure, and especially in asthmatic patients
- pulmonary haemorrhage (there have been some reports of pulmonary haemorrhage, although exact frequencies are not known)

Skin and subcutaneous tissue disorders:
• Very rare: sweating. Frequency not known: urticaria, eczema, severe skin reactions sometimes fatal including toxic epidermal necrolysis/Stevens-Johnson syndrome, Bullous dermatitis and Drug reaction with eosinophilia and systematic symptoms

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

Injury, poisoning and procedural complications:
Not known:
Potentially fatal primary graft dysfunction post cardiac transplant (see *Special Warnings and Special Precautions for Use*).

Overdose
There is no information regarding overdosage with intravenous amiodarone.
Little information is available regarding acute overdosage with oral amiodarone.
Few cases of sinus bradycardia, heart block, attacks of ventricular tachycardia, torsades de pointes, circulatory failure and hepatic injury have been reported.
In the event of overdose, treatment should be symptomatic, in addition to general supportive measures. The patient should be monitored and if bradycardia occurs beta-adrenostimulants or glucagon may be given.
Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of amiodarone, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended.
Neither amiodarone nor its metabolites are dialysable.

Pharmacological Properties
Pharmacodynamic Properties
Cordarone is a product for the treatment of tachyarrhythmias and has complex pharmacological actions. Its effects are anti-adrenergic (partial alpha and beta blocker). It has haemodynamic effects (increased blood flow and 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.

No controlled pediatric studies have been undertaken.

Pharmacokinetic Properties
Amiodarone is metabolized mainly by CYP 3A4, and also by CYP 2C8. Amiodarone and its metabolite, desethylamiodarone, exhibit a potential *in vitro* to inhibit CYP 1A1, CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, CYP 3A4, CYP 2A6, CYP 2B6 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 OCT2 substrate)). *In vivo* data describe amiodarone interactions on CYP 3A4, CYP 2C9, CYP 2D6 and P-gp substrates.
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 T1/2 of approximately 11 hours.

No controlled pediatric studies have been undertaken.

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.

Pharmaceutical Particulars
List of Excipients
Benzyl alcohol, Polysorbate and Water for Injections.

Incompatibilities
Cordarone Intravenous is incompatible with saline and should be administered solely in 5% dextrose solution. Cordarone Intravenous, diluted with 5% dextrose solution to a concentration of less than 0.6mg/ml, is unstable. Solutions containing less than 2 ampoules Cordarone Intravenous in 500ml dextrose 5% are unstable and should not be used.
The use of administration equipment or devices containing plasticizers such as DEHP (di-2-ethylhexylphthalate) in the presence of amiodarone may result in leaching out of DEHP. In order to minimise patient exposure to DEHP, the final amiodarone dilution for infusion should preferably be administered through non DEHP-containing sets.

Shelf Life
24 months.

Special Precautions for Storage
Do not store above 25°C. Store in the original container.

Nature and Contents of Container
Each carton contains six glass ampoules.

Instructions for Use/Handling
Refer to Posology and Method of Administration

Manufacturer
1. SANOFI WINTHROP INDUSTRIE
   1, rue de la Vierge
   Ambarès et Lagrave
   33565 Carbon Blanc Cedex
   FRANCE

2. DELPHARM DIJON
   6 boulevard de l'Europe
   QUETIGNY, 21800
   France

3. SANOFI S.R.L.
   Via Valcanello, 4
   03012 Anagni (FR), Italy.

Revision date:
August 2023 (Anagni alt. site)