PACKAGE LEAFLET: INFORMATION FOR THE USER

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

amiodarone hydrochloride

Is this leaflet hard to see or read? Phone 01 4035600 for help

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cordarone X is and what it is used for

Cordarone X Intravenous 150mg/3ml concentrate for solution for infusion or slow injection (called Cordarone X in this leaflet) contains a medicine called amiodarone hydrochloride. This belongs to a group of medicines called anti-arrhythmics.

It works by controlling the uneven beating of your heart (called ‘arrhythmias’). Having the injection helps your heartbeat to return to normal.

Cordarone X is normally only given in a hospital when a quick response is needed or when tablets cannot be given. Cordarone X can be used to:

- Treat uneven heartbeats where other medicines either have not worked or cannot be used.
- Treat an illness called Wolff-Parkinson-White Syndrome. This is where your heart beats unusually fast.
- Treat other types of fast or uneven heartbeats known as ‘atrial flutter’ or ‘atrial fibrillation'. Cordarone X is used only when other medicines cannot be used.
- Treat fast heartbeats which may happen suddenly and may be uneven. Cordarone X is used only when other medicines cannot be used.

2. What you need to know before you take Cordarone X

Do not take Cordarone X if:

× You are allergic (hypersensitive) to:
- iodine
- amiodarone
- any of the other ingredients of Cordarone X (listed in Section 6 below)

Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- × You have a slower than usual heartbeat (called 'sinus bradycardia') or an illness called 'sino-atrial' heart block or sick sinus syndrome.
- × You have any other problems with your heartbeat and do not have a pacemaker fitted.
- × You have ever had thyroid problems. Your doctor should test your thyroid before giving you this medicine.
- × You have severe breathing problems.
- × You have serious blood circulation problems.
- × You have very low blood pressure.
- × You are taking certain other medicines which could affect your heartbeat (see 'Other medicines and Cordarone X' below).
- × The patient is a premature baby, neonate or child under 3 years of age.
- × You are pregnant or breast-feeding (see 'Pregnancy and breast-feeding' below).

Do not have this medicine if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before having Cordarone X.

Take special care with Cordarone X
Check with your doctor, pharmacist or nurse before using this medicine if:
- ▲ You have a weak heart ('cardiomyopathy') or heart failure.
- ▲ You have low blood pressure.
- ▲ You have liver problems.
- ▲ You have any problems with your lungs including asthma.
- ▲ You have any problems with your eyesight. This includes an illness called 'optic neuritis'.
- ▲ You are about to have an operation.
- ▲ The person using the medicine is a child or adolescent.
- ▲ You currently take a medicine containing sofosbuvir for the treatment of hepatitis C as it may result in a life-threatening slowing of your heartbeat. Your doctor may consider alternative treatments. If treatment with amiodarone and sofosbuvir is needed, you may require additional heart monitoring.

If you are not sure if any of the above apply to you, talk to your doctor, nurse or pharmacist before having Cordarone X.

Warnings and precautions
There have been very rare reports of potentially life-threatening skin rashes (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis) with the use of Cordarone. Symptoms of which may include: flu-like symptoms followed by a painful red or purplish rash that spreads and blisters. If you develop any of the above you must stop taking your medicine and inform your doctor straight away (see Section 4).
Tell your doctor immediately if you are taking a medicine containing sofosbuvir for the treatment of hepatitis C and during treatment you experience:
- slow or irregular heartbeat or heart rhythm problems;
- shortness of breath or worsening of existing shortness of breath;
- chest pain;
- light-headedness;
- palpitations;
- near-fainting or fainting.

If you are on a heart transplant waiting list, your doctor may change your treatment. This is because taking amiodarone before heart transplantation has shown an increased risk of a life-threatening

complication (primary graft dysfunction) in which the transplanted heart stops working properly within the first 24 hours after surgery.

Other medicines and Cordarone X
Please tell your doctor, pharmacist or nurse if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Cordarone X can affect the way some other medicines work.
Also some medicines can affect the way Cordarone X works.

In particular, do not use this medicine and tell your doctor, if you are taking:
Medicines which may induce torsade de pointes, a heart condition which can be fatal, such as:

- Other medicines for an uneven heartbeat (such as quinidine, procainamide, disopyramide, sotalol or bretylium).
- Medicines for infections (such as intravenous erythromycin, co-trimoxazole, moxifloxacin or pentamidine injection).
- Medicines for schizophrenia (such as chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride or sertindole).
- Medicines for other mental illnesses (such as lithium, doxepin, maprotiline or amitriptyline).
- Medicines for malaria (such as quinine, mefloquine, chloroquine or halofantrine).
- Medicines used for hay fever, rashes or other allergies called antihistamines (such as terfenadine, astemizole or mizolastine).

Tell your doctor if you are taking any of the following medicines:

- Medicines for infection (such as ciprofloxacin, ofloxacin or levofloxacin).
- Medicines for heart problems called beta-blockers (such as propranolol).
- sofosbuvir, used for the treatment of hepatitis C.
- Medicines called calcium channel blockers for chest pain (angina) or high blood pressure (such as diltiazem or verapamil).
- Medicines for constipation (laxatives) such as bisacodyl or senna.
- Medicines for high cholesterol (statins) such as simvastatin or pravastatin.

The following medicines can increase the chance of you getting side effects, when taken with Cordarone X:

- Amphotericin (when given directly into a vein) used for fungal infections.
- Corticosteroids used for inflammation such as hydrocortisone, betamethasone or prednisolone.
- Water tablets (diuretics) such as furosemide.
- General anaesthetics or high dose oxygen – used during surgery.
- Tetracosactide – used to test some hormone problems.

Cordarone X may increase the effect of the following medicines:

- Warfarin, dabigatran – used for thinning the blood. Your doctor should reduce your dose of warfarin, dabigatran and monitor your treatment closely.
- Digoxin – used for heart problems. Your doctor should monitor your treatment closely and may halve your dose of digoxin.
- Phenytoin – used to treat fits.
- Flecainide - another medicine used for uneven heartbeats. Your doctor should monitor your treatment closely and may halve your dose of flecainide.
- Ciclosporin, tacrolimus and sirolimus – used to help prevent rejection of transplants.
- Medicines for impotence such as sildenafil, tadalafil or vardenafil.
- Fentanyl – used for pain relief.
- Ergotamine – used for migraines.
- Midazolam – used to relieve anxiety or to help you relax before surgery.

- Lidocaine – used as an anaesthetic.

If you are not sure if any of the above apply to you, talk to your doctor, nurse or pharmacist before taking Cordarone X.

Taking Cordarone X with food and drink
Do not drink grapefruit juice while taking this medicine. This is because drinking grapefruit juice while taking Cordarone X can increase your chance of getting side effects.

Protect your skin from sunlight
Keep out of direct sunlight while taking this medicine and for a few months after you have finished taking it. This is because your skin will become much more sensitive to the sun and may burn, tingle or severely blister if you do not take the following precautions:

- Make sure you use high factor sun cream.
- Always wear a hat and clothes which cover your arms and legs.

Pregnancy and breast-feeding
Do not use this medicine if:

- You are pregnant, might become pregnant or think you may be pregnant.
- You are breast-feeding or planning to breast-feed.

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Cordarone X contains
Iodine: This medicine contains approximately 56 mg of iodine in a 3 ml ampoule. Iodine is present in amiodarone hydrochloride, the medicine your infusion contains. Iodine can cause problems to your thyroid (see 'Tests' below).

Benzyl Alcohol: This medicine contains benzyl alcohol (20 mg/ml) as a preservative. It may cause toxic reactions and allergic reactions in infants and children up to 3 years old.

3. How to take Cordarone X

Your doctor or nurse will normally give you Cordarone X. This is because it needs to be given as an infusion into your vein in the hospital where the doctor can monitor your progress.

Having this medicine

- This medicine will be diluted before it is given to you.
- Your doctor will change you over to Cordarone X tablets as soon as possible.
- If you feel the effect of your medicine is too weak or too strong, tell your doctor, nurse or pharmacist.

If you are not sure why you are receiving Cordarone X or have any questions about how much Cordarone X is being given to you, speak to your doctor, pharmacist or nurse.

How much will be given to you
Your doctor will decide how much to give you depending on your illness.

Adults

- The usual dose is 5 mg for every kilogram of your weight given over a period of 20 minutes to 2 hours.

- You may be given another infusion of approximately 15 mg for every kilogram of your weight every 24 hours depending on your illness.
- In an emergency, your doctor may decide to give you a dose of 150 mg to 300 mg as a slow injection over 3 minutes.

Children and adolescents

- There are only limited data on the efficacy and safety in children. Your doctor will decide on an appropriate dose.

Elderly

- The doctor may give you a lower dose of Cordarone X and monitor your heart rate and thyroid function more closely.

If you use more Cordarone X than you should
Your doctor will carefully calculate how much Cordarone X you should get. Therefore, it is unlikely your doctor, nurse or pharmacist will give you too much of this medicine. But, if you think that you have been given too much or too little Cordarone X, tell your doctor, nurse or pharmacist.
The following effects may happen: feeling dizzy, faint, sick, tired or confused. Having an abnormally slow or fast heartbeat. Too much amiodarone can damage the heart and liver.

If you forget to have Cordarone X
Your doctor or nurse will have instructions on when to give you this medicine. It is unlikely that you will not be given the medicine as it has been prescribed. However, if you think you may have missed a dose, then talk to your doctor or nurse.

If you stop using Cordarone X
It is important for you to keep having Cordarone X injections until your doctor decides to stop them. If you stop using this medicine the uneven heartbeats may come back. This could be dangerous.

Tests
Your doctor may do regular thyroid tests while you are taking this medicine. This is because Cordarone X contains iodine which can cause problems to your thyroid.

Your doctor may also do other regular tests such as blood tests, chest X-rays, ECG (electrical test of your heartbeat) and eye tests both before and while you are having Cordarone X.

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

4. Possible side effects

Like all medicines, Cordarone X can cause side effects, although not everybody gets them.

Cordarone X may stay in your blood for up to a month after stopping treatment. You may still get side effects in this time.

Stop having Cordarone X and tell a doctor, nurse or pharmacist or go to a hospital straight away if:

Very rare (affects less than 1 in 10,000 people)

- You have an allergic reaction. The signs may include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.

- Your heartbeat becomes very slow or stops beating. You may also feel dizzy, unusually tired and short of breath. This may occur especially in people over 65 years old or people with other heartbeat problems.
- Your heartbeat becomes even more uneven or erratic. This can lead to a heart attack, so you should go to hospital straight away.
- You get yellowing of the skin or eyes (jaundice), feel tired or sick, loss of appetite, stomach pain or high temperature. These can be signs of liver problems or damage which can be fatal.
- Difficulty breathing or tightness in the chest, coughing which will not go away, wheezing, weight loss and fever. This could be due to inflammation of your lungs which can be fatal.
- Feeling unwell, confused or weak, feeling sick (nausea), loss of appetite, feeling irritable. This could be an illness called 'syndrome of inappropriate anti-diuretic hormone secretion' (SIADH).

Not known (frequency cannot be estimated from the available data)
- You experience a life-threatening skin reaction characterised by rash, blisters, peeling skin and pain (toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), bullous dermatitis, Drug reaction with eosinophilia and systemic symptoms (DRESS)).
- Anaphylactic reactions.
- You get loss of eyesight in one eye or your eyesight becomes dim and colourless. Your eyes may feel sore or tender and feel painful to move. This could be an illness called 'optic neuropathy or neuritis'.
- You may get more infections than usual. This could be caused by a decrease in the number of white blood cells (neutropenia).
- Severe reduction in the number of white blood cells which makes infections more likely (agranulocytosis).
- Life-threatening complication after heart transplantation (primary graft dysfunction) in which the transplanted heart stops working properly (see section 2, Warnings and precautions).

Stop having Cordarone X and see a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:
Very rare (affects less than 1 in 10,000 people)
- Headache (which is usually worse in the morning or happens after coughing or straining), feeling sick (nausea), fits, fainting, eyesight problems or confusion can occur. These could be signs of problems with your brain.

Tell your doctor as soon as possible if you have any of the following side effects:

Common (affects less than 1 in 10 people)
- Dizziness, lightheadedness, fainting. This may occur temporarily and is due to lowering of blood pressure.

Tell your doctor, nurse or pharmacist if any of the following side effects get serious or lasts longer than a few days:

Common (affects less than 1 in 10 people)
- Slightly slower heart beat.
- You have pain, swelling, irritation, reddening or skin discolouration in the area you have been injected with Cordarone X.
- Itchy, red rash (eczema).
- Decrease in sex drive.

Very rare (affects less than 1 in 10,000 people)

- Changes in the amount of liver enzymes at the beginning of treatment. This can be seen in blood tests.
- Feeling sick (nausea).
- Headache.
- Sweating.
- Hot flushes.

Not known (frequency cannot be estimated from the available data)
- Urticaria.
- Hyperthyroidism.
- Back pain.
- Pancreatitis/acute pancreatitis (sudden inflammation of the pancreas).
- Decreased appetite.
- Parkinsonism (unusual muscle movements, stiffness, shaking and restlessness.
- Confusion (delirium), seeing, hearing or feeling things that are not there (hallucinations).

Tests
Your doctor will take regular tests to check how your liver is working. Cordarone X can affect how your liver works. If this happens, your doctor will decide whether you should keep having this medicine.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance. Website: www.hpra.ie
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cordarone X

This medicine will be kept by your doctor or pharmacist in a safe place where children cannot see or reach it.

Do not use Cordarone X after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Do not store above 25˚C. Keep the ampoules in the outer carton, in order to protect from light. Only clear solutions free of particles should be used.

Discard any unused portion immediately after opening the ampoule. After dilution, use the solution immediately and discard any unused portion.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cordarone X contains
- Each 3ml ampoule contains 150mg of the active substance, amiodarone hydrochloride.
- The other ingredients are benzyl alcohol, polysorbate and water for injections.

What Cordarone X looks like and contents of the pack
- Cordarone X is a pale, yellow solution and is available as 3ml glass ampoules in cartons of 6 or 10. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
sanofi-aventis Ireland Ltd., T/A SANOFI, Citywest Business Campus, Dublin 24, Ireland
Tel: 00353 14035600
Fax: 00353 14035687
email: IEmedinfo@sanofi.com

Manufacturers
Delpharm Dijon, 6 Boulevard de l'Europe, 21800 Quetigny, France

Or

Sanofi Winthrop Industrie, 1 rue de la vierge, Ambares-et-Lagrave, 33565 Carbon Blanc Cedex, France

Or

Sanofi S.r.l., Via Valcanello, 4, 03012 Anagni (FR), Italy

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

This leaflet was last revised in February 2024

The following information is intended for healthcare professionals only:

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 section 4.4).*

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

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. Current 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 sections 4.3, 4.4 and 4.8).*
See section 6.2 for more 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 some times 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; betablockers, 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 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.
• Drugs inducing Torsade de Pointes or prolonging QT
- *Drugs inducing Torsade de pointes*
Combined therapy with drugs that may induce 'torsade de pointes' is contra-indicated *(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-antiarrhythmic 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.
Fluoroquinolones should be avoided in patients receiving Amioradone.

• Drugs lowering heart rate or causing automaticity or conduction disorders
Combined therapy with these 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 laxatives, which may cause hypokalaemia thus increasing the risk of torsade de pointes; other types of laxatives should be used.
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)

• 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 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 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*

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.

• 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:*

Amiodarone raises plasma concentrations of phenytoin by inhibition of the cytochrome P450 2C9. 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 the cytochrome P450 2D6. Therefore, flecainide dosage should be adjusted.

Combined therapy with the following drugs which prolong the QT interval is contraindicated *(see section 4.3)* due to the increased risk of torsade de pointes; for example:

Combined therapy with the following drugs is not recommended:

- There have been rare reports of QTc interval prolongation, with or without torsade de pointes, in patients taking amiodarone with fluoroquinolones. Concomitant use of amiodarone with fluoroquinolones should be avoided.

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).

• 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)*.

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 300 mg 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/m2/ 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/m2/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.

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 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.

For complete product information please refer to the Summary of Product Characteristics.