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

Cordarone X 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 used only when other medicines cannot be used. Cordarone X is used when medicines called anti-arrhythmics that help your heartbeat to return to normal help your heartbeat to return to normal.

Cordarone X is normally only given in a hospital intensive care unit (see section 4.4).

As with all medicines it is important that the minimum effective dose is used. Whilst there is no evidence that these requirements are different for the group of patients currently available data are described in section 5.1 and 5.2.

2. Before you have Cordarone X

• Treat fast heartbeats which may happen suddenly
• 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 an illness called Wolff-Parkinson-White Syndrome. This is where your heart beats unusually fast - iodine and rapidly injected. An additional 150 mg (or 2.5 mg/kg body-weight) IV dose may be considered if ventricular fibrillation persists.

3. How Cordarone X is given

Before starting Cordarone X, the patient should be restarted on intravenous infusion of 0.5mg/kg body-weight in 20 ml 5% dextrose. This may be followed by repeat infusion up to 1200mg in 250 ml of 5% dextrose. Cordarone X Intravenous should then be phased out gradually.

In extreme clinical emergency the drug may, at the discretion of the clinician, be given as a single large bolus or rapidly injected. The standard recommended dose is 5mg/kg body-weight given by intravenous infusion. Cordarone X Intravenous can be used where a rapid response is required or where oral administration is not possible.

4. Possible side effects

As with all medicines it is important that the minimum effective dose is used. Whilst there is no evidence that these requirements are different for the group of patients currently available data are described in section 5.1 and 5.2.

4.1 Therapeutic indications

Cordarone X Intravenous should only be used when facilities exist for cardiac monitoring, defibrillation, and cardiac pacing. Cordarone X Intravenous can be used where a rapid response is required or where oral administration is not possible.

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

Cordarone X Intravenous can be used where a rapid response is required or where oral administration is not possible.
- any of the other ingredients of Cordarone X (listed in Section 6 below)

Signs of an allergic reaction include: a rash, swelling 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

× You have any other problems with your heartbeat and do not have a pacemaker fitted

× You have ever had thyroid problems. Your doctor or nurse should know about this before you have 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 'Taking other medicines' below)

× The person having the medicine is a child under the age of 3 years, premature or new born baby

× 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. If you are on a heart transplant waiting list, your doctor may change your treatment. This is because taking Cordarone X 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.

4.3 Contraindications

- Sinus bradycardia and sino-atrial heart block. In patients with severe conduction disturbances (high grade AV block, bilateral or trifascicular block) or sinus node disease, Cordarone X 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;

- Hypothyroidism, heart failure and cardiomyopathy are contra-indications when using Cordarone X Intravenous as a bolus injection. (One ampoule contains approximately 56mg iodine).

- 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 torsade de points is contra-indicated (see section 4.5).

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

- Pregnancy - except in exceptional circumstances (see section 4.6).

- Lactation (see section 4.6).

All these above contra-indications do not apply to the use of amiodarone for cardiopulmonary resuscitation of shock resistant ventricular fibrillation.

4.4 Special warnings and precautions for use

Amiodarone injection contains benzyl alcohol (20 mg/ml). Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children up to 3 years old.

The administration of medications containing benzyl alcohol to newborns or premature neonates has been associated with a fatal "gasping syndrome" (symptoms include a striking onset of gasping syndrome, hypotension, bradycardia and cardiovascular collapse). As benzyl alcohol may cross the placenta, solution for injection should be used with caution in pregnancy.

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

4.5 Withdrawal

IV infusion is preferred to bolus due to the haemodynamic effects sometimes associated with rapid injection (see section 4.8). Circulatory collapse may be precipitated by too rapid administration or over dosage (atropine has been used successfully in such patients presenting with bradycardia).

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

Repeated or continuous infusion via peripheral veins may lead to injection site reactions (see section 4.6). When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended.

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

4.6 Adverse reactions

See section 4.5. Before surgery, the anaesthesiologist should be informed that the patient is taking amiodarone.

Cardiac disorders:

Caution should be exercised in patients with hypertension and uncomplicated cardiomyopathy and severe heart failure (also see section 4.3).

Amiodarone has a low pro-arrhythmic effect. Onsets of new arrhythmias or worsening of treated arrhythmias, sometimes fatal, have been reported. It is important, but difficult to differentiate a lack of efficacy of the drug from a proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects generally occur in the context of QT prolongation factors such as drug interactions and/or electrolytic disorders (see sections 4.5 and 4.6). Despite QT interval prolongation, amiodarone exhibits a low toxidromic 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-adrenerelin stimulants or glycopyrrolate 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.
Taking other medicines

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.

In particular, do not take this medicine and tell your doctor, if you are taking:

- 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, thiioridazine, fluphenazine, pimozide, haloperidol, amisulpiride 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)
- Medicines for hepatitis C treatment (such as sofosbuvir, daclatasvir, simeprevir or ledipasvir)

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)
- 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 atorvastatin

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
- Tetracostacid - used to test some hormone problems

Cordarone X may increase the effect of the following medicines:

- Warfarin – used for thinning the blood. Your doctor should reduce your dose of warfarin and monitor your treatment closely.
- Digoxin – used for heart problems. Your doctor should monitor your treatment closely and may halve your dose of digoxin.

Severe Bradycardia (see section 4.5)

Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone is used in combination with sulfonylurea in combination with another antidepressant (INH) direct acting antiretroviral (DAAs), such as dextranavir, simprevir or ledipasvir. Therefore, coadministration of these agents with amiodarone is not recommended.

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

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 sulfonylurea alone or in combination with other direct DAs.

Patients receiving these hepatitis C medicines with amiodarone, with or without other medicines that lower heart rate, should be advised to seek urgent medical advice if they experience them.

Primary graft dysfunction (PGD) post cardiac transplant

In retrospective studies, amiodarone 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 the presents as a 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 antiarythmic drug as early as possible before transplant.

Endocrine disorders (see section 4.8)

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 TSH 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, unTSH) 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 biochemical (unTSH) evidence of thyroid disease.

In patients receiving sofosbuvir, daclatasvir, simeprevir or ledipasvir, Amiodarone tablets - used to control the uneven beating of the heart called ‘arrhythmias’.

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 section 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.

Eye disorders (see section 4.8)

If blurred or decreased vision occurs, complete opthalmo logic examination including fundoscopy should be promptly performed. Appearance of optic
• Phenytoin – used to treat fits.
• Flecainide - another medicine used for uneven heartbeat. Your doctor should monitor your treatment closely and may halve your dose of flecainide.
• Ciclosporin and tacrolimus - used to help prevent rejection of transplants.
• Medicines for impotence such as sildenafil, tadalafil, vardenafil.
• Fentanyl - used for pain relief
• Ergotamine - used for migraines
• Mirtazapine - 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 take 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.

**Important information about some of the ingredients of Cordarone X**
This medicine contains:
• Iodine: Cordarone X 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: Cordarone X contains benzyl alcohol (20 mg/ml) as a preservative. It must not be given to children, premature or newborn babies. Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children up to 3 years old.

**3. How Cordarone X is given**
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

**Fluoroquinolones**
There have been rare reports of QT interval prolongation, with or without torsade de points, in patients taking amiodarone with fluoroquinolones. Concomitant use of amiodarone with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contra-indicated, see above).

**Drugs lowering heart rate, causing automaticy or conduction disorders.**
Combined therapy with the following drugs is not recommended:
• Beta blockers and certain calcium channel inhibitors (diltiazem, verapamil); potential function of negative chronotropic properties and conduction slowing effects may occur.
• Stimulant laxatives, which may cause hypokalaemia thus increasing the risk of torsade de points; 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, tetracyclines, intravenous amphotericin B.

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

**General anæsthesia**
Caution is advised in patients undergoing general anæsthesia, or receiving high dose oxygen therapy. Potentially severe complications have been reported in patients taking amiodarone undergoing general anæsthesia: bradycardia unresponsive to atropine, hypotension, disturbances of conduction, 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 X on other medicinal products**
Amiodarone and/or its metabolite, desethylamiodarone, inhibit (CYP1A2, 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 amiodarone.

**Pgp Substrates**
Amiodarone is a P-gp inhibitor. Co-administration with P-gp substrates is expected to result in an increase in their exposure.
If you have more Cordarone X than you should
Your doctor will carefully calculate how much Cordarone X you should get. Therefore it is unlikely you will not be given the medicine as it has been prescribed. However, if you think 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 having Cordarone X
It is important for you to keep having Cordarone X injections until your doctor decides to stop them. If you stop having this medicine the uneven heartbeats may come back. This could be dangerous.

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

• If you feel the effect of your medicine is too weak or too strong, tell your doctor, nurse or pharmacist.

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

• The usual dose is 5 mg for every kilogram of your weight every 24 hours depending on your illness.

Children and adolescents
There are only limited data on the efficacy and safety in children. The doctor will carefully calculate the amount of Cordarone X depending on the child's or adolescent's body weight.

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

This medicinal product must not be mixed with other preparations in the same syringe. Do not inject other preparations in the same line.

• Other drugs metabolised by CYP 3A4: examples of such drugs are lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihidroergotamine and ergotamine and zolcloline.

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.

Effect of other products on Cordarone X
CYP3A4 inhibitors and CYP2C8 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.

Grapefruit juice inhibits cytochrome P450 3A4 and may increase the plasma concentration of amiodarone. Grapefruit juice should be avoided during treatment with oral amiodarone.

Other drug interactions with amiodarone (see section 4.4)
Co-administration of amiodarone with solubilis in combination with another HEV 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 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.
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 if you:

- You have an allergic reaction. The signs may include: a rash, swelling 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 to 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 very dangerous.
- 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 very dangerous.

Frequency not known (Cannot be estimated from the available data)

- You have life-threatening irregular heart beat (Torsade de pointes).
- Symptoms include blistering or peeling of the skin around the lips, eyes, mouth, nose and genitals, flu-like symptoms and fever. This could be a condition called Stevens-Johnson syndrome.
- You have a severe blistering rash in which layers of the skin may peel off to leave large areas of raw exposed skin over the body. You may also feel generally unwell, have a fever, chills and aching muscles (Toxic Epidermal Necrolysis).
- Inflammation of the skin characterized by fluid filled blisters (bullous dermatitis).
- You have flu like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (DRESS).

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)
- Symptomatic hypotension in patients with severe heart failure.
- Symptomatic hypotension and/or bradycardia in patients with severe heart failure and/or conduction abnormalities, especially in patients with known or suspected conduction abnormalities, in patients undergoing cardioversion, in patients who have had an upper respiratory tract infection, especially in asthmatic patients.
- Severe respiratory complications (adult acute respiratory distress syndrome).
- Bronchospasm and/or apnoea in case of severe respiratory failure, and especially in asthmatic patients.

- You have flu like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (DRESS).

- You have a severe blistering rash in which layers of the skin may peel off to leave large areas of raw exposed skin over the body. You may also feel generally unwell, have a fever, chills and aching muscles (Toxic Epidermal Necrolysis).
- Inflammation of the skin characterized by fluid filled blisters (bullous dermatitis).
- You have flu like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (DRESS).

4.4 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%), very rare (≥ 0.01% and < 1%), frequency not known (cannot be estimated from the available data).

4.4.1 General disorders and administration site conditions

- Very rare (affects less than 1 in 10,000 people)
- Headache (which is usually worse in the morning or happens after coughing or straining)
- Blisters on the skin
- Poor appetite
- Swelling of your lips, face, throat or tongue
- Fainting
- 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 very dangerous.

Frequency not known (Cannot be estimated from the available data)

- You have life-threatening irregular heart beat (Torsade de pointes).
- Symptoms include blistering or peeling of the skin around the lips, eyes, mouth, nose and genitals, flu-like symptoms and fever. This could be a condition called Stevens-Johnson syndrome.
- You have a severe blistering rash in which layers of the skin may peel off to leave large areas of raw exposed skin over the body. You may also feel generally unwell, have a fever, chills and aching muscles (Toxic Epidermal Necrolysis).
- Inflammation of the skin characterized by fluid filled blisters (bullous dermatitis).
- You have flu like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (DRESS).

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)
- Symptomatic hypotension in patients with severe heart failure.
- Symptomatic hypotension and/or bradycardia in patients with severe heart failure and/or conduction abnormalities, especially in asthmatic patients.
- Severe respiratory complications (adult acute respiratory distress syndrome).
- Bronchospasm and/or apnoea in case of severe respiratory failure, and especially in asthmatic patients.

4.4.2 Skin and subcutaneous tissue disorders

- In patients taking amiodarone there have been incidental findings of bone marrow granulomas. The clinical significance of this is unknown.
- Very rare:
  - You have an allergic reaction. The signs may include: a rash, swelling 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 to 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 very dangerous.
  - 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 very dangerous.

Frequency not known (Cannot be estimated from the available data)

- You have life-threatening irregular heart beat (Torsade de pointes).
- Symptoms include blistering or peeling of the skin around the lips, eyes, mouth, nose and genitals, flu-like symptoms and fever. This could be a condition called Stevens-Johnson syndrome.
- You have a severe blistering rash in which layers of the skin may peel off to leave large areas of raw exposed skin over the body. You may also feel generally unwell, have a fever, chills and aching muscles (Toxic Epidermal Necrolysis).
- Inflammation of the skin characterized by fluid filled blisters (bullous dermatitis).
- You have flu like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (DRESS).

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)
- Symptomatic hypotension in patients with severe heart failure.
- Symptomatic hypotension and/or bradycardia in patients with severe heart failure and/or conduction abnormalities, especially in asthmatic patients.
- Severe respiratory complications (adult acute respiratory distress syndrome).
- Bronchospasm and/or apnoea in case of severe respiratory failure, and especially in asthmatic patients.
straining), feeling sick (nausea), fits, fainting, eye sight 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)
- Scaly and itching rashes (eczema)
- Dizziness, lightheadedness, fainting. This may occur temporarily and is due to lowering of blood pressure.
- Frequency not known (Cannot be estimated from the available data)
- Inflammation of the pancreas which causes severe pain in the abdomen and back (pancreatitis)
- 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).
- You get loss of eye sight in one eye or your eye sight 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'.
- Feeling extremely restless or agitated, weight loss, increased sweating and being unable to stand the heat. These could be signs of an illness called 'hyperthyroidism'.

**Very rare:** sweating.
- Frequency not known: Urticaria, weve skin reactions sometimes fatal including toxic epidermal necrolysis/Stevens-Johnson syndrome, Bullous dermatitis and Drug reaction with eosinophilia and systemic symptoms.
- Very rare: hot flushes.

**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.

**Injuries, poisoning and procedural complaints**
- Not known: Primary graft dysfunction post cardiac transplant (see section 4.4).

**Reporting of suspected adverse reactions:**
- Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefits/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card (see section 4.4).

**4.9 Overdose**

There is no information regarding overdose with intravenous amiodarone.

Little information is available regarding acute overdosage with oral amiodarone. Few cases of sinus bradycardia, heart block, attacks of ventricular tachycardia, torsade de points, 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-adrenoceptor stimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of amiodarone, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended.

Neither amiodarone nor its metabolites are dialysable.

5 Pharmacological properties

5.1 Pharmacodynamic properties

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 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 for a few hours to several days. If needed, oral therapy may be initiated concurrently at the usual loading dose.

5.2 Pharmacokinetic properties

Amiodarone is metabolised mainly by CYP3A4, and also by CYP2C8, however the pharmacokinetics of amiodarone are unusual and complex, and have not been completely elucidated. Absorption following oral administration is variable and may be prolonged, with interindividual variability. 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 biphasic 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
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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. 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 after EXP. The expiry date refers to the last day of that month.
Do not store above 25°C. Store in the original container. Only clear solutions free of particles should be used.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Cordarone X contains
• Each 3ml ampoule contains 150mg of the active substance, amiodarone hydrochloride.

The bolus IV injection of 400mg gave a terminal T½ of approximately 11 hours.
Amiodarone and its metabolite, desethylamiodarone, exhibit a potential in vitro to inhibit CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP2B6, and CYP 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 (an OCT 2 substrate). In vivo data describe amiodarone interactions on CYP3A4, CYP2C9, CYP2D6 and P-gp substrates.

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

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

6. Pharmaceutical particulars

6.1 List of excipients
Benzyl alcohol, Polysorbate and Water for Injections.

6.2 Incompatibilities
Cordarone X Intravenous is incompatible with saline and should be administered solely in 5% dextrose solution. Cordarone X Intravenous, diluted with 5% dextrose solution to a concentration of less than 0.6mg/ml, is unstable. 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.

• 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
Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK
Tel: 0845 372 7101
email: uk-medicalinformation@sanofi.com
Manufacturer
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6 Boulevard de l’Europe, 21800 Quetigny, France
Sanofi Winthrop Industrie
1 Rye de la Vierge
Ambares et Lagrave
33565 Carbon Blanc Cedex, France

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.

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6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container
Cordarone X 150mg/3ml Solution for Injection is supplied in boxes containing 6 or 10 glass ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Refer to 4.2 above.

7 Marketing authorisation holder
Sanofi
410 Thames Valley Park Drive
Reading
Berkshire
RG6 1PT
UK

8 Marketing authorisation number(s)
PL 04425/0643

9 Date of first authorisation/renewal of the authorisation
Date of first authorisation: 31 July 2010

10 Date of revision of the text
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