Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cordarone X 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Amiodarone Hydrochloride 200 mg.
Excipients: Each tablet contains 96mg lactose monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.
Round, white with a breakline on one side imprinted 200 on the other.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment should be initiated and normally monitored only under hospital or specialist supervision. Oral Cordarone X is indicated for the treatment of severe rhythm disorders only when 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 of paroxysmal nature including: supraventricular, nodal and Ventricular tachycardias, ventricular fibrillation: when other drugs cannot be used.

Cordarone is indicated for the prevention of ventricular arrhythmias in high-risk patients following myocardial infarction or in patients with clinical signs of congestive cardiac failure and/or LVEF less than 40% who are receiving appropriate cardiac failure treatment which includes ACE-inhibitors. The minimum effective dose must be used and treatment must be initiated and used only under hospital/specialist supervision.

4.2 Posology and method of administration

Cordarone X 200 Tablets are for oral administration.

Adults
It is particularly important that the minimum effective dose be used. In all cases the patient's management must be judged on the individual response and well being. The following dosage regimen is generally effective.

Initial Stabilisation
Treatment should be started with 200mg, three times a day and may be continued for 1 week. The dosage should then be reduced to 200mg, twice daily for a further week.

Maintenance
After the initial period the dosage should be reduced to 200mg daily, or less if appropriate. Rarely, the patient may require a higher maintenance dose. The scored 100mg tablet should be used to titrate the minimum dosage required to maintain control of the arrhythmia. The maintenance dose should be regularly reviewed, especially where this exceeds 200mg daily.

General Considerations

Initial dosing
A high dose is needed in order to achieve adequate tissue levels rapidly.

Maintenance
Too high a dose during maintenance therapy can cause side effects which are believed to be related to high tissue levels of amiodarone and its metabolites.

Amiodarone is strongly protein bound and has an average plasma half life of 50 days (reported range 20-100 days). It follows that sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dosage. In patients with potentially lethal arrhythmias the long half life is a valuable safeguard as omission of occasional doses does not significantly influence the overall therapeutic effect.

It is particularly important that the minimum effective dosage is used and the patient is monitored regularly to detect the clinical features of excess amiodarone dosage. Therapy may then be adjusted accordingly.

Dosage reduction / withdrawal
Side effects slowly disappear as the tissue levels fall. Following drug withdrawal, residual tissue-bound amiodarone may protect the patient for up to a month. However, the likelihood of recurrence of arrhythmia during this period should be considered.

Paediatric population
The safety and efficacy of amiodarone in children has not been established.
Currently available data are described in sections 5.1 and 5.2.

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

4.3 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 X should only be used in conjunction with a pacemaker.

Evidence or history of thyroid dysfunction.

Known hypersensitivity to iodine or to amiodarone, or any of the excipients. (One 200mg tablet contains approximately 75mg iodine).

Concomitant administration of Cordarone X with drugs which may induce torsades de pointes (*see section 4.5, Interaction with other medicinal products and other forms of interactions*).

Pregnancy: except in exceptional circumstances *(see section 4.6, Pregnancy and lactation)*.

Lactation: *see section 4.6, Pregnancy and lactation.*

4.4 Special warnings and precautions for use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine.

<u>Paediatric patients:</u>
The safety and efficacy of amiodarone in paediatric patients have not been established.
Therefore its use in paediatric patients is not recommended.

Cardiac disorders *(see section 4.8):*
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.

In the elderly, heart rate may decrease markedly.

Treatment should be discontinued in case of onset of 2nd or 3rd degree A-V block, sinoatrial block, or bifascicular block.

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.

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 (*see section 4.8*):
Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity (hypersensitivity pneumonitis, alveolar/interstitual pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonitis). Presenting features can include dyspnoea (which may be severe and unexplained by the current cardiac status), non-productive cough and deterioration in general health (fatigue, weight loss and fever). The onset is usually slow but may be rapidly progressive. Whilst the majority of cases have been reported with long term therapy, a few have occurred soon after starting treatment.

Amiodarone therapy should be re-evaluated since interstitial pneumonitis is generally reversible following early withdrawal of amiodarone.

Patients should be carefully evaluated clinically and consideration given to chest X-ray before starting therapy. During treatment, if pulmonary toxicity is suspected, this should be repeated and associated with lung function testing including where possible measurement of transfer factor. Initial radiological changes may be difficult to distinguish from pulmonary venous congestion. Pulmonary toxicity has usually been reversible following early withdrawal of amiodarone therapy, with or without corticosteroid therapy. Clinical symptoms often resolve within a few weeks followed by slower radiological and lung function improvement.Some patients can deteriorate despite discontinuing Cordarone X.

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.

Hyperthyroidism (*see sections 4.4 and 4.8*):
Hyperthyroidism may occur during amiodarone treatment, or, up to several months after discontinuation. Clinical features, such as weight loss, asthenia, restlessness, increase in heart rate, onset of arrhythmia, angina, congestive heart failure should alert the physician. The diagnosis is supported by a decrease in serum ultrasensitive TSH (usTSH) level, elevated T_3 and a reduced TSH response to thyrotropin releasing hormone (TRH). Elevation of reverse T_3 (rT_3) may also be found.
In the case of hyperthyroidism, therapy should be withdrawn. Severe cases, with clinical presentation of thyrotoxicosis, and sometimes fatal, require emergency therapeutical management. Clinical recovery usually occurs within a few months. Clinical recovery precedes the normalisation of thyroid function tests.

Courses of anti-thyroid drugs have been used for the treatment of severe thyroid hyperactivity; large doses may be required initially. These may not always be effective and concomitant high dose corticosteroid therapy (e.g. 1mg/kg prednisolone) may be required for several weeks.

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 the 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 withdrawal, however fatal cases have been reported.

Histological findings may resemble pseudo-alcoholic hepatitis, but they can be variable and include cirrhosis.

Although there have been no literature reports on the potentiation of hepatic adverse effects of alcohol, patients should be advised to moderate their alcohol intake while taking Cordarone X.

Neuromuscular disorders (*see section 4.8*):
Amiodarone may induce peripheral sensorimotor neuropathy and/or myopathy. Both these conditions may be severe, although recovery usually occurs within several months after amiodarone withdrawal, but may sometimes be incomplete.

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 is not recommended with the following drugs: beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem), stimulant laxative agents which may cause hypokalaemia.

Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system (*see section 4.8.*). Because these reactions can be delayed, patients on long-term therapy should be carefully supervised. As undesirable effects are usually dose-related, the minimum effective maintenance dose should be given.

Patients should be instructed to avoid exposure to sun and to use protective measures during therapy as patients taking Cordarone X can become unduly sensitive to sunlight, which may persist after several months of discontinuation of Cordarone X. In most cases symptoms are limited to tingling, burning and erythema of sun-exposed skin but severe phototoxic reactions with blistering may be seen. (*see section 4.8*).

Monitoring (*see sections 4.4.1 and 4.8*):
Before starting amiodarone, it is recommended to perform an ECG and serum potassium measurement. Monitoring of transaminases (*see section 4.4.1*) and ECG is recommended during treatment.

As amiodarone may induce hypothyroidism or hyperthyroidism, particularly in patients with a personal history of thyroid disorders, clinical and biological (usTSH) monitoring should be performed before starting amiodarone. This monitoring should be carried out during treatment, at six-monthly intervals, and for several months following its discontinuation. This is particularly important in the elderly. In patients whose history indicates an increased risk of thyroid dysfunction, regular assessment is recommended. Serum usTSH level should be measured when thyroid dysfunction is suspected.

In particular in the context of chronic administration of antiarrhythmic drugs, cases of increase in the ventricular fibrillation and/or pacing threshold of the pacemaker or implantable cardioverter defibrillator device have been reported, potentially affecting its efficacy. Therefore, a repeated verification of the functioning of the device before and during amiodarone treatment is recommended.

Thyroid abnormalities (*see section 4.8*):
Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T_3, free-T_4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause isolated biochemical changes (increase in serum free-T_4, free-T_3 being slightly decreased or even normal) in clinically euthyroid patients. There is no reason in such cases to discontinue amiodarone treatment.

Hypothyroidism should be suspected if the following clinical signs occur: weight gain, cold intolerance, reduced activity, excessive bradycardia. The diagnosis is supported by an increase in serum usTSH and an exaggerated TSH response to TRH. T_3 and T_4 levels may be low. Euthyroidism is usually obtained within 3 months following the discontinuation of treatment. In life-threatening situations, amiodarone therapy can be continued, in combination with L-Thyroxine. The dose of L-Thyroxine is adjusted according to TSH levels.

Anaesthesia (*see sections 4.5 and 4.8*):
Before surgery, the anaesthetist should be informed that the patient is taking amiodarone.

Primary Graft Dysfunction post cardiac transplant

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

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

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

4.5 Interaction with other medicinal products and other forms of interactions

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

- Drugs inducing *Torsade de Pointes* or prolonging QT

- *Drugs inducing Torsade de Pointes*

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

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

- *Drugs prolonging QT*

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

Fluroquinolones should be avoided in patients receiving Amiodarone.

- Drugs lowering heart rate or causing automaticity or conduction disorders

Combined therapy with these drugs is not recommended:

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

- Agents which may induce hypokalaemia:

Combined therapy with the following drugs is not recommended.

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

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

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

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

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

- General Anesthesia (see section 4.4 and 4.8)

Caution is advised in patients undergoing general anaesthesia, or receiving high dose oxygen therapy.Potentially severe complications have been reported in patients taking amiodarone undergoing general anaesthesia: bradycardia unresponsive to atropine, hypotension, conduction disorder, decreased cardiac output.
Very rare cases of severe respiratory complications (adult acuterespiratory distress syndrome), sometimes fatal, have been observed usually in the period immediately following surgery. A possible interaction with a high oxygen concentration may be implicated.

EFFECT OF CORDARONE ON OTHER MEDICINAL PRODUCTS

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

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

- PgP substrates

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

- *Digitalis*

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

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

- CYP 2C9 substrates

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

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

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

- CYP 2D6 substrates

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

- CYP P450 3A4 substrates

When such drugs are co-administered with amiodarone, an inhibitor of CYP 3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity.

- Ciclosporin: combination with amiodarone may increase ciclosporin plasma levels. Dosage should be adjusted.
- Fentanyl: combination with amiodarone may enhance the pharmacologic effects of fentanyl and increase the risk of its toxicity.
- Statins: The risk of muscular toxicity (e.g rhabdomyolysis) is increased by concomitant administration of amiodarone with statins metabolized by CYP3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolized by CYP3A4 when given with amiodarone.
- Other drugs metabolised by CYP 3A4: lidocaine, sirolimus, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, colchicine.

EFFECTS OF OTHER DRUGS ON CORDARONE

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

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

OTHER DRUG INTERACTIONS WITH AMIODARONE (see section 4.4)

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

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

4.6 Fertility, pregnancy and lactation

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

If, because of the long half life of Cordarone X, discontinuation of the drug is considered prior to planned conception, the real risk of recurrence of life threatening arrhythmias should be weighed against the unknown possible hazard for the foetus.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Blood and lymphatic system disorders:

- Very rare

Haemolytic anemia, aplastic anaemia, thrombocytopenia.

- Not known

Neutropenia, agranulocytosis.

Cardiac disorders:

- Common

Bradycardia, generally moderate and dose-related.

- Uncommon

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

- Very rare

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

- Not known

Torsade de pointes.

Endocrine disorders (*see section 4.4*):

- Common

Hypothyroidism, hyperthyroidism, sometimes fatal.

- Very rare

Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Eye disorders:

- Very common

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

- Very rare

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

Gastrointestinal disorders:

- Very common

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

- Common

Constipation.

- Uncommon

Dry mouth.

- Not known

Pancreatitis/acute pancreatitis.

General disorders:

- Not known

Granuloma, including bone marrow granuloma.

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

- Very common

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

- Common

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

- Very rare

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

Investigations:

- Very rare: increased serum creatinine.

Nervous system disorders:

- Common

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

- Uncommon

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

- Very rare

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

- Not known

Parkinsonism, parosmia.

Psychiatric disorders:

- Common

Libido decreased

- Not known

Confusional state/delirium, hallucination

Reproductive system and breast disorders:

- Very rare

Epididymo-orchitis, impotence.

Respiratory, thoracic and mediastinal disorders:

- Common

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

- Not known

Pulmonary haemorrhage

- Very rare

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

Skin and subcutaneous tissue disorders:

- Very common:

Photosensitivity (*see section 4.4*)

- Common

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

- Very rare

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

- Not known:

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

Vascular disorders:

- Very rare

Vasculitis.

Immune system disorders:

- Not known

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

Metabolism and nutrition disorders:

- Not known

Decreased appetite.

Musculoskeletal and Connective Tissue Disorders:

- Not known

Lupus like syndrome.

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

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

4.9 Overdose

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

In the event of overdose treatment should be symptomatic, gastric lavage may be employed to reduce absorption in addition to general supportive measures.

The patient should be monitored and if bradycardia ensues, beta-adrenostimulants or glucagon may be given.

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

Neither amiodarone or its metabolites is dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: CO1B D01
Pharmacotherapeutic group: Antiarrhythmics, Class III

Amiodarone slows sinoatrial, atrial and nodal conduction and increases the refractory period at the atrial, nodal and ventricular levels but does not alter intraventricular conduction. There is also slowing in conduction and prolongation of refractory periods in accessory atrioventricular pathways.

Amiodarone has anti-adrenergic (non-competitive alpha and beta blocker) effects. It inhibits the metabolic and biochemical effects of catecholamines on the heart and inhibits Na+ and K+ activated ATP-ase.

Amiodarone has anti-ischaemic and haemodynamic effects. It causes a moderate drop in peripheral resistance and decrease in heart rate leading to a reduction in oxygen intake. It causes an increase in coronary output due to a direct effect on the smooth muscle of the myocardial arteries. Cardiac output is maintained due to a decrease in aortic pressure and peripheral resistance.

A univariate analysis (EMIAT) suggested that all-cause mortality is reduced on amiodarone treatment in patients with an ejection fraction less than 30%, with arrhythmia on the initial Holter, on beta-blocker treatment, and with an increased initial heart rate.

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

Following oral administration absorption is slow and variablewith an approximate mean of 50%, and may be prolonged due to enterohepatic cycling. Following single administration, peak plasma concentrations are reached after 3-7 hours. Therapeutic effects are usually observed after one week (from a few days to two weeks depending on the loading dose). Due to the above characteristics, loading doses should be used in order to obtain rapidly the tissue levels necessary to have a therapeutic effect.

Amiodarone has a large but variable volume of distribution because of extensive accumulation in various sites (adipose tissue, highly perfused organs such as the liver, lung and spleen). 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.

The major metabolite is desethylamiodarone. Amiodarone has a long half-life and shows considerable individual variability (from 20 to 100 days). During the first days of therapy, the drug accumulates in almost all tissues, especially the adipose tissue. Elimination occurs after a few days and steady-state plasma concentration is reached between one and several months depending upon the individual patient.

Renal excretion is minimal; excretion is mainly via the bile and the faeces.

After treatment discontinuation, the elimination continues over several months; the persistence of a pharmacodynamic effect over 10 days to one month should be taken into account.

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

5.3 Preclinical safety data

In a 2-years carcinogenicity study in rats, amiodarone caused an increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinical relevant exposures. Since mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is proposed for this type of tumour induction. In the mouse, carcinomas were not observed, but a dose-dependent thyroid follicular hyperplasia was seen.

These effects on the thyroid in rats and mice are most likely due to effects of amiodarone on the synthesis and/or release of thyroid gland hormones. The relevance of these findings to man is low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone
Maize starch
Colloidal silicon dioxide
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep the blister in the outer carton.

6.5 Nature and contents of container

Cordarone X 200mg tablets are supplied in PVC/aluminium blister packs of 28 and 30 tablets further packed in cardboard cartons.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0540/142/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 November 1984

Date of last renewal: 24 August 2007

10 DATE OF REVISION OF THE TEXT

March 2022