Cordarone

Amiodarone 200mg

Scored Tablet

[sanofi logo]

Composition:
Cordarone 200 contains 200mg of amiodarone hydrochloride.

Pharmaceutical Form
Tablet.
Round, white tablet with a breakline on one side, imprinted with 200 and “heart-shaped” symbol on the other.

Clinical Particulars
Therapeutic Indications
Treatment should be initiated and normally monitored only under hospital or specialist supervision. Oral Cordarone 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 of paroxysmal nature including: supraventricular, nodal and ventricular tachycardias, ventricular fibrillation: when other drugs cannot be used.

Posology and Method of 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
The minimum effective dosage should be used according to individual response. It may range between 100mg daily to 400mg daily. Cordarone may be given on alternative days (200mg may be given every other day where 100mg are recommended daily); therapeutic windows have been also recommended (2 days a week): they are possible due to the prolonged therapeutic action of Cordarone.

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 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.

Pediatric population
The safety and efficacy of amiodarone in children has not been established.

Elderly
As with all patients it is important that the minimum effective dose is used. Whilst there is no evidence that dosage requirements are different for this group of patients they may be more susceptible to bradycardia and conduction defects if too high a dose is employed. Particular attention should be paid to monitoring thyroid function. (see *Contraindications, Special Warnings and Special Precautions for Use, and Undesirable Effects*).
Cordarone Tablet 200mg is for oral administration.

Contraindications
Sinus bradycardia and sino-atrial heart block. In patients with severe conduction disturbances (high grade AV block, bifascicular or trifascicular block) or sinus node disease, Cordarone should be used only in conjunction with a pacemaker.
Evidence or history of thyroid dysfunction. Thyroid function tests should be performed in all patients prior to therapy.
Known hypersensitivity to iodine or to amiodarone, or to any of the excipients. (One 200mg tablet contains approximately 75mg iodine).
The combination of Cordarone with drugs which may induce torsades de pointes is contraindicated (see *Interactions with Other Medicinal Products and Other Forms of Interaction*).
Pregnancy - except in exceptional circumstances (see *Pregnancy and Lactation*).
Lactation (see *Pregnancy and Lactation*).

Special Warnings and Special Precautions for Use
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system (see *Undesirable Effects*). Because these reactions may be delayed, patients on long-term treatment should be carefully supervised. As undesirable effects are usually dose-related, the minimum effective maintenance dose should be given.
Before surgery, the anaesthetist should be informed that the patient is taking amiodarone (see *Interactions with Other Medicinal Products and Other Forms of Interaction and Undesirable Effects*).

Cardiac disorders (see *Undesirable Effects*)
Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances, Cordarone treatment should be withdrawn. If necessary 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.
Oral Cordarone is not contraindicated in patients with latent or manifest heart failure but caution should be exercised as, occasionally, existing heart failure may be worsened. In such cases, Cordarone may be used with other appropriate therapies.
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, sino-atrial 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 *Interactions with Other Medicinal Products and Other Forms of Interaction, and Undesirable Effects*). Despite QT interval prolongation, amiodarone exhibits a low torsadogenic activity.
Before starting amiodarone, it is recommended to perform an ECG and serum potassium measurement. Monitoring of ECG is recommended during treatment.
Amiodarone may increase the defibrillation threshold and/or pacing threshold in patients with an implantable cardioverter defibrillator or a pacemaker, which may adversely affect the efficacy of the device. Regular tests are recommended to ensure the proper function of the device after initiation of treatment or change posology.

Severe Bradycardia (see *Undesirable Effects*) :
Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone is used in combination with sofosbuvir alone or in combination with another hepatitis C virus (HCV) direct acting antiviral (DAA), such as daclatasvir, simeprevir, or ledipasvir. Therefore, coadministration of these agents with amiodarone is not recommended.
If concomitant use with amiodarone cannot be avoided, it is recommended that patients are closely monitored when initiating sofosbuvir alone or in combination with other DAAs.
Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for at least 48 hours in an appropriate clinical setting after initiation of the concomitant treatment with sofosbuvir.
Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofosbuvir alone or in combination with other direct DAAs.
Patients receiving these hepatitis C medicines with amiodarone, with or without other medicines that lower heart rate, should be warned of the symptoms of bradycardia and heart block and should be advised to seek urgent medical advice if they experience them.

Endocrine disorders (see *Undesirable Effects*)
Amiodarone may induce hypothyroidism or hyperthyroidism, particularly in patients with a personal history of thyroid disorders. Clinical and biological [including ultrasensitive TSH (usTSH)] monitoring should be performed prior to therapy in all patients. 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.
Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T3, free-T4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of levothyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum free-T4, free-T3 being slightly decreased or even normal) in clinically euthyroid patients. There is no reason in such cases to discontinue amiodarone treatment if there is no clinical or further biological (usTSH) evidence of thyroid disease.

Hypothyroidism
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. T3 and T4 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 levothyroxine. The dose of levothyroxine is adjusted according to TSH levels.

Hyperthyroidism

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 usTSH level, an elevated T3 and a reduced TSH response to thyrotropin releasing hormone. Elevation of reverse T3 (rT3) may also be found. In the case of hyperthyroidism, therapy should be withdrawn. Clinical recovery usually occurs within a few months, although severe cases, sometimes resulting in fatalities, have been reported. 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.

Eye disorders (see Undesirable Effects)
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.

Hepato-biliary disorders (see *Undesirable Effects*)
Amiodarone may be associated with a variety of hepatic effects, including cirrhosis, hepatitis,jaundice and hepatic failure. Some fatalities have been reported, mainly following long-term therapy, although rarely they have occurred soon after starting treatment particularly after Cordarone intravenous. It is advisable to monitor liver function particularly transaminases before treatment and six monthly thereafter.
At the beginning of therapy, elevation of serum transaminases which can be in isolation (1.5 to 3 times normal) may occur. These may return to normal with dose reduction, or sometimes spontaneously.
Isolated cases of acute liver disorders with elevated serum transaminases and/or jaundice may occur; in such cases treatment should be discontinued.
There have been reports of chronic liver disease. Alteration of laboratory tests which may be minimal (transaminases elevated 1.5 to 5 times normal) or clinical signs (possible hepatomegaly) during treatment for longer than 6 months should suggest this diagnosis. Routine monitoring of liver function tests is therefore advised. Abnormal clinical and laboratory test results usually regress upon cessation of treatment, but 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.

Nervous system disorders (see *Undesirable Effects*)
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.

Respiratory, thoracic and mediastinal disorders (see *Undesirable Effects*)
Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity (hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonitis. Presenting features can include dyspnea (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.
Patients should be carefully evaluated clinically and consideration given to chest X-rays 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.

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

Severe bullous reactions
Life-threatening or even fatal cutaneous reactions Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (see *Undesirable Effects*). If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present amiodarone treatment should be discontinued immediately.

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

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

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

Drug interactions (see *Interactions with Other Medicinal Products and Other Forms of Interaction*)
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.
Increased plasma levels of flecainide have been reported with co-administration of amiodarone.
The flecainide dose should be reduced accordingly and the patient closely monitored.

Interactions with Other Medicinal Products and Other Forms of Interaction
Some of the more important drugs that interact with amiodarone include warfarin, digoxin, phenytoin and any drug which prolongs the QT interval.
Amiodarone raises the plasma concentrations of CYP 2C9 substrates such as oral anticoagulants (warfarin) and phenytoin by inhibition of CYP 2C9. The dose of warfarin should be reduced accordingly. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended. Phenytoin dosage should be reduced if signs of overdosage appear, and plasma levels may be measured.
Administration of Cordarone to a patient already receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels. Clinical, ECG and biological monitoring is recommended and digoxin dosage should be halved. A synergistic effect on heart rate and atrioventricular conduction is also possible.
Combined therapy with the following drugs which prolong the QT interval is contra-indicated (see *Contra-indications*) due to the increased risk of torsades de pointes; for example:
- Class Ia anti-arrhythmic drugs e.g. quinidine, procainamide, disopyramide
- Class III anti-arrhythmic drugs e.g. sotalol, bretylium
- intravenous erythromycin, co-trimoxazole or pentamidine injection
- some anti-psychotics e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpiride and sertindole
- lithium and tricyclic anti-depressants e.g. doxepin, maprotiline, amitriptyline
- certain antihistamines e.g. terfenadine, astemizole, mizolastine
- anti-malarials e.g. quinine, mefloquine, chloroquine, halofantrine
- moxifloxacin
- drugs lowering heart rate or causing automaticity or conduction disorders

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

Fluoroquinolones
There have been rare reports of QTc interval prolongation, with or without torsades de pointes, in patients taking amiodarone with fluoroquinolones.
Concomitant use of amiodarone with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contraindicated, see above)

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

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

Flecainide
Given that flecainide is mainly metabolised by CYP 2D6, by inhibiting this isoenzyme, amiodarone may increase flecainide plasma levels; it is advised to reduce the flecainide dose by 50% and to monitor the patient closely for adverse effects. Monitoring of flecainide plasma levels is strongly recommended in such circumstances.

Interaction with substrates of other CYP 450 isoenzymes
In vitro studies show that amiodarone also has the potential to inhibit CYP 1A2, CYP 2C19 and CYP 2D6 through its main metabolite. When co-administered, amiodarone would be expected to increase the plasma concentration of drugs whose metabolism is dependent upon CYP 1A2, CYP 2C19 and CYP 2D6.

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

HCV direct acting antiviral
Coadministration of amiodarone with sofosbuvir alone or in combination with another HCV direct acting antiviral (such as daclatasvir, simeprevir, or ledipasvir) is not recommended as it may lead to serious symptomatic bradycardia. The mechanism for this bradycardia effect is unknown.
If coadministration cannot be avoided, cardiac monitoring is recommended**Pregnancy and Lactation**
Pregnancy
There are insufficient data on the use of amiodarone during pregnancy in humans to judge any possible toxicity. However, in view of its effect on the foetal thyroid gland, amiodarone is contraindicated during pregnancy, except in exceptional circumstances.
If, because of the long half-life of amiodarone, discontinuation of the drug is considered prior to planned conception, the real risk of reoccurrence of life threatening arrhythmias should be weighed against the possible hazard for the foetus.

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

Effects on Ability to Drive and Use Machines
The ability to drive or operate machinery may be impaired in patients with clinical symptoms of amiodarone-induced eye disorders.

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

Blood and lymphatic system disorders:
• Very rare:
- haemolytic anemia
- aplastic anaemia
- thrombocytopenia.
• Frequency not known: In patients taking amiodarone there have been incidental findings of bone marrow granulomas. Neutropenia, agranulocytosis.

Cardiac disorders:
• Common: bradycardia, generally moderate and dose-related.
• Uncommon:
- onset or worsening of arrhythmia, sometimes followed by cardiac arrest (see *Special Warnings and Special Precautions for Use and Interactions with Other Medicinal Products and Other Forms of Interaction*).
- conduction disturbances (sinoatrial block, AV block of various degrees) (see *Special Warnings and Special Precautions for Use*)
• Very rare: marked bradycardia or sinus arrest in patients with sinus node dysfunction and/or in elderly patients.
• Frequency not known:

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

Endocrine disorders (see *Special Warnings and Special Precautions for Use*):
• 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 *Special Warnings and Special Precautions for Use*).

Gastrointestinal disorders:
• Very common: benign gastrointestinal disorders (nausea, vomiting, dysgeusia) usually occurring with loading dosage and resolving with dose reduction.
• Frequency Not known: pancreatitis/ acute pancreatitis, dry mouth, constipation
General disorders and administration site conditions:
• Frequency not known: Granuloma, including bone marrow granuloma

Hepato-biliary disorders: (see *Special Warnings and Special Precautions for Use*)
• 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.

Immune system disorders:
• Frequency not known: angioedema (there have been some reports of angioedema, although exact frequencies are not known), anaphylactic/anaphylactoid reaction including shock.

Metabolism and nutrition disorders:
• Frequency not known: Decreased appetite

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

Investigations:
• Very rare: increase in blood 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 *Special Warnings and Special Precautions for Use*).
• Very rare:
- cerebellar ataxia, for which regression usually occurs after reduction of dose or withdrawal

- benign intracranial hypertension (pseudo- tumor cerebri)
- headache
- vertigo.
• Frequency not known: parkinsonism, parosmia

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

Reproductive system and breast disorders:
• Very rare:
- epididymo-orchitis
- impotence.
• Frequency not known: Libido decreased

Respiratory, thoracic and mediastinal disorders:
• Common: pulmonary toxicity [hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia (BOOP)], sometimes fatal (see *Special Warnings and Special Precautions for Use*).
• Very rare:
- bronchospasm in patients with severe respiratory failure and especially in asthmatic patients
- surgery (possible interaction with a high oxygen concentration) (see *Special Warnings and Special Precautions for Use and Interactions with Other Medicinal Products and Other Forms of Interaction*).
- Pulmonary haemorrhage (there have been some reports of pulmonary haemorrhage, although exact frequencies are not known)

Skin and subcutaneous tissue disorders:
• Very common: photosensitivity (see *Special Warnings and Special Precautions for Use*).
• 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.
• Very rare:
- erythema during the course of radiotherapy
- skin rashes, usually non- specific
- exfoliative dermatitis
- alopecia
• Not known: urticaria, eczema, severe skin reactions sometimes fatal including toxic epidermal necrolysis/Stevens-Johnson syndrome, Bullous dermatitis and Drug reaction with eosinophilia and systematic symptoms

Vascular disorders:
• Very rare: vasculitis.

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

Overdose
Little information is available regarding acute overdosage with oral amiodarone. Few cases of sinus bradycardia, heart block, attacks of ventricular tachycardia, torsades de pointes, circulatory failure and hepatic injury have been reported.
In the event of overdose treatment should be symptomatic, gastric lavage may be employed to reduce absorption in addition to general supportive measures. The patient should be monitored and if bradycardia occurs beta-adrenostimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of amiodarone, adequate and

prolonged surveillance of the patient, particularly cardiac status, is recommended. Neither amiodarone nor its metabolites are dialysable.

Pharmacological Properties

Pharmacodynamic Properties

Amiodarone hydrochloride is an antiarrhythmic.

No controlled pediatric studies have been undertaken.

Pharmacokinetic Properties

Amiodarone is metabolized mainly by CYP 3A4, and also by CYP 2C8. Amiodarone and its metabolite, desethylamiodarone, exhibit a potential *in vitro* to inhibit CYP 1A1, CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, CYP 3A4, CYP 2A6, CYP 2B6 and 2C8. Amiodarone and desethylamiodarone have also a potential to inhibit some transporters such as P-gp and organic cation transporter (OCT2) (One study shows a 1.1% increase in concentration of creatinine (a OCT2 substrate)). *In vivo* data describe amiodarone interactions on CYP 3A4, CYP 2C9, CYP 2D6 and P-gp substrates.

Amiodarone is strongly protein bound and the plasma half-life is usually of the order of 50 days. However there may be considerable inter-patient variation; in individual patients a half-life of less than 20 days and a half-life of more than 100 days have been reported. High doses of Cordarone, for example 600mg/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half-life of the drug, a maintenance dose of only 200mg/day, or less is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half-life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by Cordarone.

No controlled pediatric studies have been undertaken.

Preclinical Safety Data

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

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

Pharmaceutical Particulars

List of Excipients

Lactose monohydrate, Maize starch, Povidone, Colloidal anhydrous silica, Magnesium stearate.

Incompatibilities

Not applicable.

Shelf Life

36 months.

Special Precautions for Storage

The tablets should be protected from light.

Nature and Contents of Container

Cordarone 200 tablets are supplied in blister packs of 30 tablets packed in cardboard cartons.

Instructions for Use/Handling

Not applicable.

Manufacturer

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