Cordarone®
Amiodarone HCl
200 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each tablet contains:
Amiodarone (NN) hydrochloride …….. 200 mg
Excipient: Lactose, Maize starch, Polyvidone, Colloidal silica, Magnesium stearate, and Purified water

PHARMACEUTICAL FORM

Tablet of 200 mg Amiodarone
White to slightly cream, round, scored tablets with break-line, engraved with a "heart-shaped" symbol and "200" on one side, blank on the other side

PHARMACOLOGICAL PROPERTIES

Anti arrhythmic properties :

- Reduced sinus automaticity leading to bradycardia unresponsive to atropine administration.
- Non-competitive alpha and beta adrenergic inhibition.
- Slowing in sino-atrial, atrial and nodal conduction, *which is increased in proportion to rhythm rapidity*
- No change in intra ventricular conduction.
- Increased in refractory period and decrease of myocardial excitability at the atrial, nodal and ventricular levels.
- Slowing in conduction and prolongation of refractory periods in accessory atrioventricular pathways.

Other properties:

- Moderate drop in peripheral resistance and decrease in heart rate leading to a reduction of oxygen intake.
- Increase of coronary output due to a direct effect on myocardial arteries smooth muscle.
- Maintenance of cardiac output due to a decrease in aortic pressure and peripheral resistance.

Others

- No significant negative inotropic effect.

Pharmacokinetics properties

Amiodarone has a slow transit and a high affinity to tissues.
Oral bioavailability has varied between 30 and 80% along with individual patients (mean value around 50%). Following single administration, peak plasma concentrations are reached after 3 to 7 hours. Therapeutic effects are usually obtained after one week (from a few days to two weeks), according to the loading dose.

Amiodarone has a long half-life including considerable inter-patient 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 1 to several months depending on each individual patient. Due to the above characteristics, loading doses should be used in order to rapidly obtain the impregnation of tissues that is necessary to have a therapeutic effect.

Iodine is partly removed from the molecule and is found in urine as Iodide; this corresponds to 6mg/24 hours when 200mg of amiodarone is given daily. The remaining part of the molecule, thus including most of iodine, is eliminated in the faces following hepatic excretion.

The negligible renal excretion allows the administration or usual doses in patients with renal failure.

Following treatment discontinuation, the elimination continues ever several months; the persistence or a residual effect over 10 days to one month should be taken into account.

Amiodarone is mainly metabolized by cytochrome CYP3A4, and also by cytochrome CYP2C8. Amiodarone and its metabolite, desethylamiodarone, are potential in vitro inhibitors of cytochromes CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP2A6, CYP2B6 and CYP2C8. Amiodarone and desethylamiodarone can also inhibit transport proteins such as P-gp and organic cation transporter 2 (OCT2). One study showed a 1.1% increase in creatinine concentration (an OCT2 substrate).

In vivo data describe an interaction between amiodarone and CYP3A4, CYP2C9, CYP2D6 and P-gp substrates.

Preclinical safety data

In a 2-year carcinogenicity study in rats, amiodarone caused an increase in the number of thyroid follicular tumors (adenomas and/or carcinomas) in both sexes at clinically relevant exposures.
Since mutagenicity findings were negative, an epigenetic rather than genotoxic mechanism has been suggested to explain induction of this type of tumor.
Studies in mice did not show any carcinomas, but dose-dependent thyroid follicular hyperplasia was observed. These effects on the thyroid in rats and mice were probably due to the effects of amiodarone on the synthesis and/or release of thyroid hormones. These findings have little relevance to humans.

CLINICAL PARTICULARS

Therapeutic indications

Cordarone® is indicated only for the treatment of severe rhythm disorders, not responding to other therapy or when other treatment cannot be used:

- Atrial rhythm disorders (conversion of fibrillation or flutter, and maintenance of sinus rhythm following conversion).
- Modal rhythm disorders
- Ventricular rhythm disorders (life-threatening ventricular tachycardia solves, prevention of ventricular tachycardia attacks or ventricular fibrillation episodes.
- Rhythm disorders associated with Wolf-Parkinson-While syndrome.

In view of its pharmaceutical properties, amiodarone is indicated in the above rhythm disorders especially when they are associated with an underlying heart disease (coronary insufficiency, heart failure).

DOSAGE AND ADMINISTRATION

Initial stabilization: usual dosage is 600mg daily and may be continued for 8 to 10 days.
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 alternate (200 mg may be given every other day where 100mg are recommended daily);

CONTRAINDICATION

This medicine is contraindicated in the following situations:

- Sinus bradycardia and sino-atrial block not corrected by a pacemaker;
- Sinus disease not corrected by a pacemaker (risk of sinus arrest);
- High-degree conduction disorders not corrected by a pacemaker;
- Hyperthyroidism due to its possible exacerbation by amiodarone;
- Known hypersensitivity to iodine or amiodarone;
- The last 6 months of pregnancy;
- Breast-feeding
- Combination with medicines that can induce torsades de pointes:
  - class la antiarrhythmics (quinidine, hydroquinidine, disopyramide, etc).
  - class III antiarrhythmics (sotalol, dofetillide, ibutilide, etc),
  - sultopride,
- other medicines, such as bepridil, cisapride, diphemanil, erythromycin IV, mizolastine, sparfloxacin, etc. (cf. Interactions with other medicinal products and other forms of interaction).

This medicine IS NOT GENERALLY RECOMMENDED in combination with:

- Injectable diltiazem,
- Halofantrine, pentamidine, moxifloxacine,
- Certain neuroleptics (thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, amisulpride, tiapride, primozide, haloperidol, droperidol), and with beta-blockers other than sotalol and esmolol (cf. Interactions with other medicinal products and other forms of interaction).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warning

An ECG must be performed before starting treatment

- Slowing of heart rate may be accentuated in elderly patients.
- The electrocardiogram is modified under amiodarone. This "cordaronic" modification consists of a prolongation in QT reflecting a repolarisation prolongation, possibly with the appearance of a U wave; this is a sign of therapeutic impregnation and not of toxicity.
- The onset of 2nd or 3rd-degree atrioventricular block, sino-atrial block or bifascicular block should lead to suspension of treatment. 1st degree atrioventricular block should lead to increased monitoring.
- The presence of iodine in the medicinal product falsifies certain thyroid tests (binding of radioactive iodine, PBI); however, thyroid function assessment is still possible (T3, T4, TSHus).
- Such a proarrhythmic effect may occur especially if there are factors that promote QT interval prolongation, such as certain drug combinations and hypokalemia (see Sections 4.5 and 4.8). The risk of drug-induced torsades de pointes seems lower with amiodarone compared with other anti-arrhythmic agents in patients with the same degree of QT interval prolongation.
- Combination (cf. Interactions with other medicinal products and other forms of interaction) with:
  - beta-blockers other than sotalol (contraindicated combination) and esmolol (combination requiring precautions for use).
  - Verapamil and ditiazem, should only be considered in the prevention of life-threatening ventricular arrhythmias.

Due to the presence of lactose, this medicinal product is contraindicated in the event of congenital galactosaemia, glucose and galactose malabsorption syndrome or lactase deficiency.

The onset of dyspnoea or a dry cough, alone or associated with a deterioration in general condition, should suggest the possibility of pulmonary toxicity and requires X-ray (Cf. Undesirable effects).

Severe skin disorders
Life-threatening or even fatal cutaneous reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis may occur. If patients experience signs or symptoms indicative of these conditions (e.g. progressive skin rash with blisters or mucosal lesions), amiodarone treatment should be discontinued immediately.

Severe bradycardia and conduction disorders
Cases of severe, potentially life-threatening bradycardia and conduction disorders have been observed when amiodarone is used in combination with sofosbuvir in combination with another antiviral (DAA) acting directly on the hepatitis C virus (HCV), such as daclatasvir, simeprevir, or ledipasvir.

Bradycardia has usually occurred within a few hours to a few days, but cases with a longer time to onset have been observed, mostly up to 2 weeks after initiation of anti-HCV treatment.

Amiodarone should only be used in patients treated with medicines containing sofosbuvir if they are intolerant or contraindicated to other antiarrhythmic drugs.

If concomitant use of amiodarone is deemed necessary, it is recommended that patients undergo inpatient cardiac monitoring for the first 48 hours of co-administration, following which outpatient monitoring or heart rate self-monitoring should be performed daily for at least the first 2 weeks of treatment.

In view of the long half-life of amiodarone, cardiac monitoring as described above should also be performed in patients who have stopped amiodarone within the last few months and who are to start treatment with medicines containing sofosbuvir alone or in combination with other DAAs.

All patients who currently or have recently used amiodarone in combination with medicines containing sofosbuvir should be warned of the symptoms of bradycardia and conduction disturbances, and they should be advised of the need for urgent medical attention if they experience these symptoms.

PRECAUTION
Precautions for use
Electrolyte balance disturbance and, in particular, hypokalaemia: it is important to take into account situations that may be associated with hypokalaemia since the latter can promote the onset of proarrhythmic effects.
Hypokalaemia should be corrected prior to administration of amiodarone.
The undesirable effects mentioned below are usually related to excessive drug levels; they can be avoided or their severity minimized by carefully seeking the minimum maintenance dosage.
Patients should be advised to avoid exposure to sun or to use sun protection during treatment.
Amiodarone can cause thyroid anomalies (cf Undesirable effects).
Assay of TSH is recommended in all patients before treatment and then regularly throughout treatment - for example, every 6 months - and several months after its withdrawal.
TSH levels should be measured in the event of clinical suspicion of dysthyroidism (cf. Undesirable effects).
In children, the safety and efficacy of amiodarone have not been evaluated by controlled clinical trials.
Regular monitoring of liver function (transaminase levels) is useful to screen for liver damage caused by amiodarone (cf. Undesirable effects).

Anaesthesia
Before surgery, the anaesthetist must be informed that the patient is treated with amiodarone.
Chronic treatment with amiodarone may lead to exacerbation, in terms of undesirable effects, of the haemodynamic risks of general or local anaesthetics.
These concern, in particular, bradycardiac and hypotensive effects, reduced cardiac output and conduction disturbances.
In addition, a few cases of acute respiratory distress have been observed immediately after surgery in patients treated with amiodarone. Consequently, close monitoring is recommended during artificial ventilation of such patients (Cf. Undesirable effects).

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
A number of antiarrhytmics drugs depress cardiac automatism, conduction and contractility.
The combination of antiarrhytmics from different classes can provide a beneficial therapeutic effect, but it usually VERY DELICATE, requiring close clinical and ECG monitoring. The combination of antiarrhytmics inducing torsades de pointes (such as amiodarone) is CONTRAINDICATED.
The combination of antiarrhytmics from the same class is NOT RECOMMENDED, apart from in exceptional cases, due to the increased risk of cardiac undesirable effects. Combination with medicines with negative inotropic, bradycardiac and/or atrioventricular conduction slowing drugs is DELICATE and requires close clinical and ECG monitoring.

Effect of amiodarone on other medicinal products
Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP1A1, CYP1A2, CYP3A4, CYP2C9, CYP2D6 and P-glycoprotein and may increase exposure of their substrates.
Given the long-acting effect of amiodarone, these interactions may be observed for several months after treatment discontinuation.

Contraindicated combinations
Medicinal products that can induce torsades de pointes:
- Class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),
- Class III antiarrhythmics (dofetilide, ibutilide, sotalol),
- Other medicinal products such as: bepridil, cisapride, diphemanil, erythromycin IV, mizolastine, vincamine IV,
- Sultopride
  Increased risk of ventricular arrhythmia and in particular, torsades de pointes.
- Sparfloxacin
  Risk of torsades de pointes due to a prolongation in QT interval (addition of the electrophysiological effects).

Inadvisable combinations
+ Sofosbuvir
Co-administration of amiodarone with treatments containing sofosbuvir may result in severe symptomatic bradycardia. Use only if no alternative treatment is available. Close monitoring is recommended when these medicinal products are co-administered (see section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

+ Neuroleptics liable to induce torsades de pointes:

Some phenothiazine neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides neuroleptics (amisulpride, sulpiride, tiapride), butyrophenones neuroleptics (droperidol, haloperidol), other neuroleptics (pimozide).

Increased risk of ventricular Arrhytmia and, in particular, torsades de pointes.

+ Halofantrine, moxifloxacin, pentamidine

Increased risk of ventricular arrhythmia and, in particular, torsades de pointes. If possible, suspend the non-antibiotic torsadogenic drug. If the combination cannot be avoided, prior control of QT and constant electrocardiographic monitoring.

+ Injectable diltiazem

Risk of bradycardia and atrioventricular block. If this combination cannot be avoided, only administer under close clinical and constant electrocardiographic monitoring.

+ Beta-blockers (other than sotalol and esmolol)

Contractility, automatism and conduction disturbances (suppression of compensatory sympathetic mechanisms).

Combination requiring precautions for use

+ Oral anticoagulants

Increased anticoagulant effect and haemorrhagic risk.

More frequent control of prothrombin rate and monitoring of INR. Adjustment of oral anticoagulant dosage during treatment with amiodarone and after its withdrawal.

+ Cyclosporin

Increase in blood levels of ciclosporin due to a reduction in its hepatic metabolism with a risk of nephrotoxic effects.

Assay of blood ciclosporin concentrations, monitoring of kidney function and adjustment of dosage during combination with amiodarone and after its withdrawal.

+ Oral Diltiazem

Risk of bradycardia and atrioventricular block, particularly in the elderly. Clinical and electrocardiographic monitoring.

+ Digitalis drugs

Depression of automatism (excessive bradycardia) and atrioventricular conduction disturbances. In the event of use digoxin, increased blood digoxin levels due to reduced digoxin clearance.

Clinical and electrocardiographic monitoring, and if necessary monitoring of blood digoxin levels and adjustment of digoxin dosage.

+ Esmolol

Contractility, automatism and conduction disturbances (suppression of compensatory sympathetic mechanisms). Clinical and electrocardiographic monitoring.

+ **Potassium-lowering drugs: potassium-lowering diuretics (alone or in combination), stimulant laxatives, glucocorticoids (systemic route), tetracosactide, amphotericin B (IV route).**

Increased risk of ventricular arrhythmia and, in particular, torsades de pointes (hypokalemia is a predisposing factor).

Clinical, laboratory and electrocardiographic monitoring.

+ Phenytoin

Increased in plasma concentrations of phenytoin with signs of overdose, and in particular, neurological signs (reduced hepatic metabolism of phenytoin).

Clinical monitoring, control of plasma concentrations of phenytoin and if necessary, adjustment of the latter's dosage.

+ Bradycardiac agents: bradycardiac calcium channel blockers (diltiazem, verapamil), beta-blockers (except sotalol), clonidine, guanfacin, digitalis drugs, mefloquine, anticholinesterases drugs (donezepil, galantamine, rivastigmine, tacrine, ambemonium, pyridostigmine, neostigmine).

Increased risk of ventricular arrhythmia and, in particular, torsades de pointes.

Clinical and electrocardiographic monitoring.

+ Simvastatin

Increased risk of undesirable effects (dose-dependent), such as rhabdomyolysis (reduce hepatic metabolism of the cholesterol-lowering drug).
Do not exceed a dosage of 20 mg/d simvastatin.
If the therapeutic goal is not achieved at this dosage, use another statin not concerned by this type of interaction.

+ Statins

The risk of muscle toxicity (e.g. rhabdomyolysis) is increased when amiodarone is co-administered with statins metabolized by CYP3A4 such as simvastatin, atorvastatin and lovastatin.
The use of another statin not affected by this type of interaction is recommended.

+ Tacrolimus

Increased blood concentrations of tacrolimus by inhibition of its metabolism by amiodarone.
Tacrolimus blood concentration assay, control of renal function, and tacrolimus dosage adjustment when used in combination and at the discontinuation of amiodarone.

+Lidocaine

Risk of increased plasma concentrations of lidocaine with the possibility of neurological and cardiac adverse effects, by decreased hepatic metabolism of amiodarone.
Clinical monitoring, ECG and possible check of the plasma concentrations of lidocaine. If necessary, adjustment of the dosage of lidocaine during the treatment with amiodarone and after its discontinuation.

+Other molecules metabolised by CYP3A4 (sirolimus, sildenafil, midazolam, dihydroergotamine, ergotamine, colchicine, triazolam)

Amiodarone, a CYP3A4 inhibitor, increases the plasma concentrations of these molecules, which may lead to a possible increase in their toxicity.

PREGNANCY AND LACTATIONS

Pregnancy

Animal studies have not revealed any teratogenic effect. In the absence of any teratogenic effect in animals, no malformative effect is expected in humans.
In fact, to date, substances responsible for malformations in humans have been revealed to be teratogenic in animals in the course of properly conducted studies in both species.
Clinically, no sufficiently relevant data are currently available to be able to assess a potential malformative effect of amiodarone when it is administered during the first three months of pregnancy.
Since the foetal thyroid begins to blind iodine from 14 weeks after the last menstrual period, no effects on the foetal thyroid are expected in the event of administration prior to this.
Iodine overload related to the use of this medicine after this time can lead to foetal hypothyroidism, which may be biological or even clinical (goitre).
Consequently, the use of this medicine is contraindicated after the first 3 months of pregnancy.

Lactation

Amiodarone and its metabolite, along with iodine, cross into breast milk at concentrations greater than those in maternal plasma. Due to the risk of hypothyroidism in the newborn infant, breast-feeding is contraindicated in the event of treatment with this medicine.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Not relevant

UNDESIRABLE EFFECTS

Ocular signs

Corneal micro-deposits, which are almost constant in adults, usually remain localized to the area under the pupil and do not contraindicate continuation of treatment. In exceptional cases these may be accompanied by perception of colored halos in dazzling light or sensations of mistiness.
Composed of complex lipid deposits, corneal micro-deposits are always entirely reversible on discontinuation of treatment.
A few cases of optic neuropathy (optic neuritis) with blurred vision, reduced vision and papillary oedema at the fundus of the eye have been reported. The outcome may be a more or less severe reduction in visual acuity. The relationship with amiodarone does not appear to have been established at the current time. However in the event of any other obvious cause, it is recommended that treatment be suspended.

Skin and subcutaneous tissue disorders

Photosensitisation. Subjects are advised to avoid exposure to sun (and ultraviolet rays in general) during treatment.
Cases of erythema have also been reported during radiotherapy.
Cases of skin rashes - generally not very specific - and a few cases of exfoliative dermatitis have been reported, without the relationship with the medicine having been clearly established.
Exceptional cases of lilac or slate-grey colored pigmentation of the skin may occur at high daily dosages prescribed for a long period of time; after treatment withdrawal, this pigmentation is slow to disappear (10 to 24 months).
Not known: Eczema, urticaria, severe skin reactions sometimes fatal including toxic epidermal necrolysis/Stevens- Johnson syndrome, Bullous dermatitis and Drug reaction with eosinophilia and systematic symptoms

Thyroid signs

In the absence of any clinical signs of dysthyroidism, a "dissociated" thyroid hormone level (increase in T4, T3 normal or slightly reduced) does not warrant withdrawal of treatment.
Hypothyroidism has a classic form: weight gain, apathy, drowsiness and clear elevation in TSH signal its diagnosis. Withdrawal of the treatment leads to a gradual return to normal thyroid function within a period of 1 to 3 months; this withdrawal is not essential. If the indication so warrants, amiodarone may be continued, combining it with L-thyroxine-based substitutive opotherapy, with TSH levels acting as a guide for the dosage.
Hyperthyroidism is more misleading: with few symptoms (slight unexplained weight loss, reduction in anti-angina and/or antiarrhythmic efficacy); psychiatric forms in the elderly, or even thyrotoxicosis. A reduction in ultra-sensitive TSH levels confirms the diagnosis.
It is essential to suspend amiodarone: this is usually enough to trigger clinical recovery within a period of 3 to 4 weeks. Severe cases can lead to the patient's death, making it necessary to urgently instigate appropriate treatment. If the thyrotoxicosis is worrying, either in itself or due to its effects on the precarious myocardial balance, the inconstant efficacy of synthetic anti-thyroid drugs leads to straightforward corticosteroid therapy (1 mg/kg) being recommended, for a sufficiently long period of time (3 months).
Cases of hyperthyroidism have been reported as long as several months following discontinuation of amiodarone.

Pulmonary signs

Cases of diffuse interstitial or alveolar pneumopathy and bronchiolitis obliterans organizing pneumonia (BOOP) have been reported. The onset of effort dyspnoea - either isolated or associated with a deterioration in general condition (fatigue, weight loss, febricula) - requires radiological control and, if necessary, suspension of treatment. These types of pneumopathy can actually develop into pulmonary fibrosis.

Early withdrawal of amiodarone-associated or not with corticosteroid therapy-leads to a regression in the disturbances. Clinical signs usually disappear in 3 or 4 weeks. Radiological and function improvement is usually slower (several months).
A few cases of pleurisy, generally associated with interstitial pneumopathies, have been reported.
A few cases of bronchospasm have been reported, particularly in asthmatic patients.
A few cases of acute respiratory distress syndrome, sometimes fatal, have been observed, sometimes immediately following surgery (a possible interaction with high doses of oxygen has been suggested).

Neurological effects
These are rare:
- The prolonged administration of amiodarone can cause sensory, motor or mixed peripheral neurophaties and myopathies. These may occur after just a few months of treatment, but sometimes after several years. They are generally reversible on treatment withdrawal. However, this recovery may be incomplete, very slow and occur only several months after treatment discontinuation.
- Other disturbances reported: tremor or other extra-pyramidal symptoms, cerebellar-type ataxia, exceptional benign intra-cranial hypertension, sleep disturbances including nightmares.

Hepatic signs
Cases of liver disease have been reported; these cases have been diagnosed by an elevation in serum transaminase levels. In fact, the following have been reported:
- Isolated and generally moderate (1.5 to 3 times normal values) elevation in transaminase levels, regressing following a reduction in the dosage or even spontaneously.
- Exceptionally (a few isolated cases), acute liver disease with hypertransaminasaemia and/or jaundice, sometimes fatal, requiring suspension of treatment.
- Rare cases of chronic liver disease during prolonged treatment. The histology is that of pseudo-alcoholic hepatitis. The discretion of the clinical and laboratory picture (inconstant hepatomegaly, hypertransaminasaemia between 1.5 and 5 times normal levels) warrants regular monitoring of liver function.

  Hypertransaminasaemia - even moderate-occuring after treatment for more than 6 months may suggest a diagnosis of chronic liver disease. The clinical and laboratory disturbances usually regress after treatment is withdrawn. A few cases of an irreversible outcome have been reported.

Cardiac effects
Generally moderate, dose-dependent bradycardia. In certain cases (sinus dysfunction, elderly patients), marked bradycardia and, more exceptionally, sinus arrest have been reported.
Rarely: conduction disturbances (sino-atrial block, atrioventricular block of varying degrees).
The arrythmogenic effect of amiodarone is weak, less than that of most antiarrhythmic drugs and generally occurs in some drug combinations (cf. Interaction with other medicinal products and other forms of interaction) or electrolyte balance disturbances.
Not known: Torsades de pointes

Immune system disorders:
- Not known: angioneurotic edema

General disorders:
- Not known: Granuloma, essentially bone marrow granuloma, have been reported.

Gastrointestinal disorders:
- Benign gastrointestinal disturbances (nausea, vomiting, dysgeusia), usually occurring during initial treatment and disappearing when the dosage is reduced.
- Not known: Pancreatitis/ acute pancreatitis, dry mouth, constipation

Metabolism and nutrition disorders
- Not known : Decreased appetite

Blood and lymphatic system disorders
- Very rare: thrombocytopenia, haemolytic anaemia, aplastic anaemia.
- Not known: Neutropenia, agranulocytosis

Psychiatric disorders
- Common: Decreased libido
- Not known: Delirium (including confusion), hallucinations

Nervous system disorders:
- Not known: Parkinsonism, parosmia

Musculoskeletal and connective tissue disorders:
- Not known: Lupus syndrome.

Injury, poisoning and procedural complications
- Not known: Potentially fatal primary graft dysfunction post cardiac transplant (See Precaution).

Miscellaneous effects
- A few cases of epididymitis have been reported. The relationship with the medicine does not appear to have been established. A few rare cases of alopecia have been observed.
- A few isolated cases, expressed in a variety of ways, have been observed in a context suggesting a hypersensitivity reaction: vascularitis, renal impairment with a moderate elevation in creatinine, thrombopaenia.

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 reaction via farmakovigilans@kalventis.com
and Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan. Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/.

OVER DOSAGE
There is little documentation available on the acute administration of high doses of amiodarone. A few cases of sinus bradycardia, ventricular arrhythmia – in particular, torsades de pointes – and liver damage have been reported. Treatment should be symptomatic. Given the kinetics of the product, monitoring for a sufficiently long period of time – particularly cardiac monitoring – is recommended. Amiodarone and its metabolites cannot be dialyzed.

Do not use later than the date of expiry date.

SPECIAL PRECAUTIONS FOR STORAGE
Store at temperature below 30°C.

HARUS DENGAN RESEP DOKTER

Reg.No.DKL1421205810A1

Pack size: Box of 3 blisters of 10 tablets

Manufactured and Registered by:
PT Kalventis Sinergi Farma,
Jakarta – Indonesia

Under license from:
Sanofi Winthrop Industrie, France

Date of text revision:
20 September 20 2025

Based on Amiodarone- FR SmPC (30 Dec 2021), Addition of PV contact information & Undesirable Effects

Informasi untuk pasien
Cordarone® 200 mg tablet
Amiodaron hidroklorida

Baca seluruh isi leaflet ini dengan seksama sebelum Anda mulai mengkonsumsi obat ini karena mengandung informasi penting untuk Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, hubungi dokter atau apoteker Anda.
- Obat ini telah diresepkan untuk Anda. Jangan berikan kepada orang lain. Produk ini dapat berdampak negatif bagi mereka, sekalipun gejala yang Anda dan mereka alami serupa.
- Jika Anda mengalami efek samping, konsultasikan kapada dokter atau apoteker Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Lihat bagian 4.

Apa yang tercantum pada leaflet ini:

1. Apa itu Cordarone® dan kegunaannya

Cordarone® digunakan untuk mengatasi masalah irama jantung yang serius jika pengobatan lain tidak berhasil atau tidak bisa digunakan. Ini termasuk:

1. Jantung berdetak terlalu cepat di bagian serambi jantung (atrium) dan menjaga irama jantung tetap normal setelah konversi jantung (proses mengembalikan irama jantung yang tidak normal menjadi irama yang normal).
2. Gangguan irama nodal (masalah pada denyut jantung yang disebabkan oleh gangguan pada nodus atau simpul jantung. Ini bisa membuat jantung berdetak terlalu cepat atau terlalu lambat).
3. Jantung berdetak terlalu cepat di bagian bilik jantung (ventrikel).
4. Sindrom Wolf-Parkinson-White, suatu kondisi langka yang bisa menyebabkan irama jantung tidak teratur atau bahkan berhenti.

Amiodarone diindikasikan pada gangguan irama jantung seperti di atas terutama bila berhubungan dengan penyakit jantung yang mendasarinya seperti pada insufisiensi koroner (kondisi ketika aliran darah ke otot jantung berkurang atau terhenti, sehingga otot jantung tidak mendapatkan cukup oksigen. Hal ini dapat menyebabkan rasa sakit dada atau bahkan kerusakan pada otot jantung), juga pada kondisi gagal jantung (terjadi ketika jantung tidak dapat memompa darah dengan baik, sehingga tubuh tidak mendapatkan cukup oksigen dan nutrisi. Ini bisa membuat seseorang merasa lelah, sesak napas, dan dapat menyebabkan penumpukan cairan dalam tubuh).

2. Apa yang perlu Anda ketahui sebelum mengkonsumsi Cordarone®

Obat ini tidak boleh digunakan dalam situasi berikut:

- Jika anda memiliki penyakit sinus (gangguan irama jantung yang membuat jantung berdetak terlalu cepat. Ini dapat menyebabkan gejala seperti denyut jantung tidak teratur), mengalami denyut jantung lambat (sinus bradikardia) dan sumbatan jantung sinoatrial (kondisi ketika sinyal listrik di jantung terhalang atau tersumbat, sehingga membuat irama jantung menjadi tidak teratur atau lambat. Hal ini dapat mengakibatkan detak jantung yang tidak normal) tanpa protesa jantung (jantung buatan yang digunakan untuk menggantikan jantung yang sakit atau rusak. Jantung buatan ini membantu tubuh memompa darah dengan lebih baik, sehingga orang yang memilikinya bisa menjalani kehidupan yang lebih sehat);
- Jika Anda mengalami gangguan konduksi jantung tingkat tinggi tanpa protesa jantung;
- Hipertiroidisme (penyakit kelenjar tiroid) karena dapat memperburuk kondisi dengan amiodaron;
- Jika Anda alergi (hipersensitivitas) terhadap yodium atau amiodaron;
- Jika Anda hamil lebih dari 3 bulan;
- Wanita yang sedang menyusui;
- Jika Anda mengonsumsi obat lain yang dapat menginduksi *torsades de pointes* (gangguan irama jantung yang serius)*;*
- Jika Anda sedang mengkonsumsi obat lain, pastikan penggunaannya dengan Cordarone® tidak dikontraindikasikan (lihat bagian "Obat lain dan Cordarone®").

Peringatan dan perhatian

Peringatan

Pemeriksaan elektrokardiogram/EKG (tes medis yang merekam aktivitas listrik di dalam jantung) harus dilakukan sebelum memulai pengobatan.

- Perlambatan detak jantung yang mungkin lebih sering terjadi pada pasien lanjut usia.
- Perpanjangan interval QT
- Timbulnya kelainan irama jantung
- Adanya kandungan yodium dalam produk obat yang dapat memberikan hasil palsu pada tes tiroid tertentu
- Efek proaritmia (munculnya gangguan irama jantung yang baru atau memburuknya gangguan irama jantung yang sudah ada sebelumnya yang terjadi setelah pemberian terapi), terutama jika terdapat faktor yang mendorong pemanjangan interval QT
- Kombinasi (lihat Interaksi dengan produk obat lain dan bentuk interaksi lainnya) dengan:
  - beta-blocker selain sotalol (kombinasi yang dikontraindikasikan) dan esmolol (kombinasi yang memerlukan kewaspadaan dalam penggunaannya).
  - Verapamil dan ditiazem hanya boleh dipertimbangkan dalam penggunaan untuk pencegahan gangguan irama jantung pada bilik jantung (ventrikel) yang mengancam jiwa.

Jika dokter Anda memberi tahu Anda bahwa Anda memiliki intoleransi terhadap beberapa gula misalnya laktosa, galaktosa, hubungi dokter Anda sebelum Anda mengkonsumsi obat ini.

Jika timbul sesak nafas atau batuk kering, tunggal atau disertai perburukan kondisi umum, ini menunjukkan kemungkinan adanya efek samping pada paru dan memerlukan sinar-X. (Lihat Efek yang tidak diinginkan)

Kelainan kulit yang parah
Dapat terjadi reaksi alergi kulit yang parah. Jika pasien mengalami ruam kulit progresif disertai lepuh atau lesi pada permukaan kulit, pengobatan amiodarone harus segera dihentikan.

Bradikardia parah (perlambatan detak jantung) dan gangguan konduksi
Kasus perlambatan detak jantung dan gangguan konduksi yang parah dan berpotensi mengancam jiwa telah diamati dalam kombinasi amiodarone dengan sofosbuvir dan kombinasi dengan antivirus lain (DAA) yang bekerja langsung pada virus hepatitis C (HCV), seperti daclatasvir, simeprevir, atau ledipasvir.

Pasien yang sedang atau baru saja mengkonsumsi amiodarone dikombinasikan dengan obat-obatan yang mengandung sofosbuvir harus diperingatkan mengenai gejala bradikardia dan gangguan konduksi, dan diberitahu mengenai perlunya perhatian medis segera jika pasien mengalami gejala-gejala ini.

Perhatian
Gangguan keseimbangan elektrolit khususnya hipokalemia (kurangnya kadar kalium dalam darah), harus diobati sebelum pemberian amiodarone.

Amiodarone dapat menyebabkan kelainan tiroid (lihat Efek yang tidak diinginkan).

Pemeriksaan *Thyroid Stimulating Hormomne* (TSH) sebelum pengobatan dan kemudian secara rutin selama pengobatan (misalnya setiap 6 bulan) dan beberapa bulan setelah penghentian pengobatan dianjurkan jika ada kecurigaan klinis terhadap distiroidisme (gangguan fungsi kelenjar tiroid)

Pemeriksaan rutin kadar transaminase bermanfaat untuk melihat kerusakan hati yang disebabkan oleh amiodarone (lihat Efek yang tidak diinginkan).

Anak-anak
Toleransi dan efikasi obat ini tidak diketahui.

Anastesi
Ahli anastesi harus diberitahu bahwa pasien sedang dilakukan pengobatan dengan amiodarone sebelum dilakukannya operasi.

Transplantasi
Dalam penelitian retrospektif, penggunaan amiodarone sebelum transplantasi jantung telah dikaitkan dengan adanya peningkatan risiko disfungsi cangkok primer (PGD), yaitu komplikasi transplantasi jantung yang mengancam jiwa yang muncul sebagai disfungsi bilik kiri, kanan, atau keduanya (biventrikular) yang terjadi dalam 24 jam pertama setelah operasi transplantasi tanpa penyebab sekunder yang dapat diidentifikasi (lihat Efek yang Tidak Diinginkan).

Pasien yang akan dilakukan transplantasi jantung harus dipertimbangkan untuk mengonsumsi alternatif lain dari obat antiaritmia sebelum dilakukan transplantasi.

Obat-obatan lain dan Cordarone®

Obat ini tidak boleh digunakan jika Anda sudah mengonsumsi obat-obatan berikut ini:

- Kombinasi dengan obat-obatan yang menyebabkan *torsades de pointes* (gangguan irama jantung yang serius): quinidine, hydroquinidine, disopyramide, sotalol, dofetilide, ibutilide, sultopride.

- Obat lain, seperti:
  - o bepridil,
  - o cisapride,
  - o diphemanil,
  - o eritromisin intravena,
  - o mizolastine,
  - o sparfloksasin,

Anda tidak boleh mengkonsumsi obat ini jika Anda sedang mengkonsumsi obat-obatan berikut kecuali disarankan oleh dokter Anda:
- injeksi diltiazem;
- antiparasit tertentu (halofantrine, moxifloxacin, pentamidin);
- neuroleptik tertentu (amisulfride, chlorpromazine, cyamemazine, droperidol, haloperidol, levomepromazine, primozide, sulpiride, tiapride, tioridazin, trifluoperazin);
- beta bloker (selain sotalol dan esmolol)
- sofosbuvir

Kombinasi yang memerlukan tindakan pencegahan untuk digunakan
- antikoagulan oral
- diltiazem oral
- obat digitalis
- esmolol
- obat penurun kalium: diuretic penurun kalium (tunggal atau dengan kombinasi, pencahar stimulant, glukokortikoid (rute sistemik), tetracosactide, amphotericin B (rute IV)
- phenytoin
- agen bradikardia (perlambatan detak jantung): penghambat saluran kalsium bradikardia (diltiazem, verapamil), beta-bloker (kecuali sotalol), clonidine, guanfacin, obat digitalis, mefloquine, obat antikolinesterase (donezepil, galantamine, rivastigmine, tacrine, ambemonium, pyridostigmine, neostigmine).
- statin (simvastatin, atorvastatin, lovastatin)
- CORDARONE dapat meningkatkan efek obat-obatan berikut: ciclosporin, tacrolimus dan sirolimus yang digunakan untuk membantu mencegah penolakan transplantasi, lidokain, sildenafil, midazolam, dihidroergotamin, ergotamin, kolkisin, triazolam.

Kehamilan dan menyusui

Kehamilan
Jangan mengkonsumsi obat ini jika Anda sedang hamil lebih dari 3 bulan, yaitu sejak trimester ke-2 kehamilan.
Mintalah saran dokter atau apoteker Anda sebelum mengkonsumsi obat apa pun.

Menyusui
Anda tidak boleh menyusui jika Anda sedang mengkonsumsi obat ini.
Mintalah saran dokter atau apoteker Anda sebelum mengkonsumsi obat apa pun.

3. Cara mengkonsumsi Cordarone®

Dosis dan durasi pengobatan
Dosis bervariasi antara satu orang dengan orang lain.
Umumnya:

- 3 tablet per hari pada awal pengobatan selama 8 sampai 10 hari,
- kemudian, pada hari-hari berikutnya (dosis pemeliharaan), dari 1/2 tablet sampai 2 tablet per hari, yang dapat diberikan secara bergantian dengan alternatif 200 mg diberikan dua hari sekali sementara 100 mg direkomendasikan diberikan setiap hari.

Penggunaan pada anak-anak
Data efikasi dan keamanan obat ini pada anak-anak sangat terbatas. Dokter Anda akan menentukan dosis yang sesuai.
Oleh karena itu, Anda harus benar-benar mematuhi petunjuk dokter Anda dan tidak boleh mengubah dosis tanpa nasihat medis.
Demikian pula, Anda tidak boleh menghentikan pengobatan tanpa berkonsultasi dengan dokter Anda.

Metode administrasi
Anda harus mengkonsumsi tablet dengan sedikit air (rute oral).
Anda dapat mengkonsumsi sebelum, saat, atau di luar waktu makan. Menghancurkan tabletnya tidak akan mengubah keefektifannya.

Cordarone® tablet mudah dikenali dari 2 logo yang terukir di permukaannya.
Jika dokter Anda telah meresepkan setengah tablet (satu kali atau lebih per hari), bagilah seperti yang ditunjukkan di bawah ini.
Cordarone® tablet memiliki garis tengah: Anda dapat dengan mudah membaginya menjadi 2 bagian yang sama.
Untuk membaginya menjadi 2 bagian, tekan permukaan yang rata dengan ibu jari Anda.

Jika Anda mengkonsumsi lebih banyak Cordarone® dari yang seharusnya:
Konsultasikan dengan dokter atau apoteker Anda segera.

Jika Anda lupa mengkonsumsi Cordarone®:
Ada kalanya lupa mengkonsumsi tablet, hal ini tidak membuat Anda terkena risiko tertentu. Jangan mengambil dosis ganda untuk menggantikan dosis yang terlupa.

4. Efek samping yang mungkin terjadi

Gejala pada mata
Endapan mikro di kornea, endapan lipid kompleks, neuropati optik dengan penglihatan kabur, penurunan penglihatan dan edema papiler di fundus mata

Kelainan kulit dan jaringan subkutan
Reaksi kulit yang berlebihan terhadap matahari (fotosensitifitas), bercak merah pada kulit, kulit kemerahan, dermatitis eksfoliatif (kondisi inflamasi yang ditandai dengan reaksi kemerahan dan pengelupasan kulit mencapai lebih dari 90% luas permukaan tubuh), perubahan warna kulit menjadi ungu atau abu-abu pada dosis harian tinggi yang diresepkan untuk jangka waktu lama (setelah penghentian pengobatan pigmentasi ini perlahan hilang (10 hingga 24 bulan)).

Tidak diketahui : Eksim (penyakit kulit dengan gejala ruam merah di kulit dan terasa gatal), urtikaria (biduran atau bentol-bentol pada kulit), nekrolisis epidermal toksik/sindrom Stevens-Johnson (reaksi alergi kulit yang parah), dermatitis bulosa (lepuhan pada kulit) dan reaksi obat dengan eosinofilia dan gejala sistematis.

Gejala tiroid
Kadar hormon tiroid yang tinggi (hipertiroidisme) atau rendah (hipotiroidisme) di dalam tubuh

Gejala pada paru
Difus interstitial (kondisi yang menyebabkan peradangan atau jaringan parut di paru) atau penyakit paru alveolar (infeksi menyebabkan peradangan pada kantong-kantong udara (alveoli) di salah satu atau kedua paru-paru)), bronkiolitis obliterans dengan pneumonia pengorganisasian (BOOP) atau inflamasi paru-paru yang mempengaruhi bronkiolus dan alveoli, sesak napas, pleuritis (peradangan pada selaput pembungkus organ paru-paru atau pleura). Bronkospasme (kontraksi abnormal otot polos bronkus, yang mengakibatkan penyempitan akut dan terhalangnya jalan napas) khususnya pada pasien asma, sindrom gangguan pernapasan akut.

Efek neurologis
Jarang : neuropati (kelainan saraf) dan miopati (kelainan otot) perifier sensorik, motorik, atau keduanya
Gangguan lain yang dilaporkan: tremor atau gejala gangguan gerak lainnya, ataksia tipe serebelar (kelainan di otak yang menyebabkan gangguan gerak dan keseimbangan tubuh), hipertensi intrakranial jinak (peningkatan tekanan darah di tengkorak), gangguan tidur termasuk mimpi buruk.

Gejala pada hati
Penyakit hati dengan peningkatan kadar transaminasi (enzim hati) dalam darah

Efek pada jantung
Bradikardia (perlambatan detak jantung), disfungsi sinus pada pasien lanjut usia.
Jarang: gangguan konduksi (blok sino-atrial (kelainan pada ritme normal jantung, yang dikenal sebagai blok jantung), blok atrioventrikular (terhambatnya aliran listrik yang mengatur denyut jantung) dengan derajat yang bervariasi)).
Tidak diketahui: *Torsades de pointes*

Gangguan sistem imun
Tidak diketahui : edema angioneurotik (pembengkakan yang mirip urtikaria yang terjadi pada area kulit, laring (kotak suara), dan area lainnya)

Gangguan umum
Tidak diketahui : Granuloma (benjolan kecil pada jaringan tubuh yang terbentuk dari kumpulan sel-sel darah putih) sumsum tulang

Gangguan saluran cerna
- Gangguan saluran cerna jinak (mual, muntah, dysgeusia/perubahan pada indera perasa), biasanya terjadi pada awal pengobatan dan hilang bila dosis dikurangi.
- Tidak diketahui: Pankreatitis/ pankreatitis akut, mulut kering, sembelit

Gangguan metabolisme dan nutrisi
Tidak diketahui : penurunan nafsu makan

Gangguan pada sistem peredaran darah dan limfatik
Sangat jarang: penurunan jumlah keping darah (trombositopenia), kelainan darah yang ditandai dengan penghancuran berlebihan jumlah sel darah merah (anemia hemolitik), kelainan darah yang disebabkan oleh ketidakmampuan sumsum tulang untuk memproduksi sel darah dalam jumlah yang cukup (anemia aplastik).
Anda berisiko terkena infeksi lebih banyak dari biasanya. Hal ini mungkin disebabkan oleh penurunan jumlah sel darah putih (neutropenia), penurunan jumlah sel darah putih yang parah, yang membuat kemungkinan terjadinya infeksi (agranulositosis).

Gangguan kejiwaan
Umum: penurunan libido
Tidak diketahui: Keadaan bingung/delirium, halusinasi (melihat, mendengar atau merasakan hal2 yang sebenarnya tidak ada)

Gangguan sistem saraf
Tidak diketahui: Parkinsonisme (gejala gangguan saraf yang menyebabkan gangguan pergerakan), parosmia (gangguan penciuman)

Gangguan muskuloskeletal dan jaringan ikat
Tidak diketahui: Sindrom Lupus.

Cedera, keracunan dan komplikasi prosedural
Tidak diketahui: Disfungsi cangkok primer yang berpotensi fatal pasca transplantasi jantung (Lihat Tindakan Pencegahan).

Efek lain
Epididimitis (peradangan pada saluran sperma)
Jarang : alopesia (rambut rontok / kebotakan).
Reaksi hipersensitivitas: vaskularitis (peradangan pada pembuluh darah), gangguan ginjal dengan peningkatan kreatinin sedang, trombopenia (jumlah keping darah (trombosit) rendah atau di bawah normal)

Pelaporan efek samping

Jika Anda atau anak Anda mendapatkan efek samping, bicarakanlah dengan dokter, apoteker atau perawat Anda. Termasuk kemungkinan efek samping yang tidak tercantum dalam brosur ini.

Anda juga dapat melaporkan efek samping secara langsung ke Industri Farmasi dengan kontak berikut farmakovigilans@kalventis.com.

5. Dengan melaporkan efek samping Anda dapat membantu memberikan informasi tentang keamanan obat ini.Bagaimana cara menyimpan Cordarone®

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tertera pada kotak. Tanggal kedaluwarsa mengacu pada hari terakhir bulan itu.

Simpan di bawah suhu 30°C.

Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana cara membuang obat yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan

6. Isi dari kemasan dan informasi lainnya

Apa kandungan Cordarone®

- Zat aktifnya adalah: amiodaron hidroklorida. Satu tablet mengandung 200 mg amiodaron hidroklorida
- Bahan lainnya adalah: *lactose, maize starch, polyvidone, colloidal silica, magnesium stearate, purified water*

Seperti apa Cordarone® dan isi kemasannya
Tablet Cordarone® berbentuk bulat diukir dengan simbol berbentuk "hati" dan "200" pada permukaannya, berwarna putih-krem dengan masa rata-rata 350.0mg
Dus berisi 3 blister dengan masing-masing blister berisi 10 tablet

HARUS DENGAN RESEP DOKTER
Dus, 3 blister @ 10 tablet selaput – No. Reg: DKL1421205810A1

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