For the use only of a Registered Medial Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack

AMIODARONE TABLETS I.P.

CORDARONE®
CORDARONE® X

Active Moiety/Active Ingredient
Amiodarone

Therapeutic or Pharmacological Class
Antiarrhythmics, Class III

Pharmaceutical Form(s)
Tablets; 100 mg, 200 mg

COMPOSITION

Cordarone®
Each uncoated tablet contains:
Amiodarone Hydrochloride I.P. …..100mg

Cordarone® X
Each uncoated tablet contains:
Amiodarone Hydrochloride I.P. ….200mg

THERAPEUTIC INDICATIONS

- Treatment should be initiated and normally monitored only under hospital or specialist supervision. Oral amiodarone 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.

DOSAGE & 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 stabilization: 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 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 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.

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, Undesirable effects).*

Cordarone® X and Cordarone® is for oral administration.

CONTRAINDICATIONS

- Sinus bradycardia, sinoatrial block, and sick sinus syndrome (risk of sinus arrest), severe atrioventricular conduction disorders, unless a pacemaker is fitted.
- Combined therapy with drugs which may induce “torsade de pointes” (see section Interactions) Thyroid dysfunction
- Known hypersensitivity to iodine or to amiodarone or to any of the excipients
- Pregnancy, unless exceptional circumstances (see section Pregnancy)
- Lactation (see section lactation)

WARNINGS

Cardiac disorders *(see Adverse Reactions):*

The pharmacological action of Amiodarone induces ECG changes such as QT prolongation (related to prolonged repolarisation) with the possible development of U-waves However these changes do not

reflect toxicity. Heart rate may decrease markedly in elderly patients. Treatment should be discontinued in case of onset of 2nd or 3 rd degree A-V block, sinoartrial block, or bifascicular block.
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 are more rarely reported with amiodarone than with the other antiarrhythmic agents, and generally occur in the context of QT prolonging factors such as drug interactions and / or electrolytic disorders (see interactions and adverse reactions). Despite QT interval prolongation, amiodarone exhibits a low torsadogenic activity.

Severe Bradycardia *(see Interactions)*
Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone is used in combination with sofosbuvir 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 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.

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

PGD is a life-threatening complication of heart transplantation 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 Adverse Reactions).

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

Hyperthyroidism *(see Precautions and section Adverse Reactions)*
Hyperthyroidism may occur during amiodarone treatment or, upto several months after discontinuation. Clinical features, usually slight, such as weight loss, onset of arrhythmia, angina, congestive heart failure should alert the physician. The diagnosis is supported by a clear decrease in serum ultrasensitive TSH (us TSH) level.
In which case amiodarone should be withdrawn. Recovery usually occurs within a few months following withdrawal of treatment; clinical recovery precedes the normalisation of thyroid function tests. Severe cases, with clinical presentation of thyrotoxicosis, and sometimes fatal, require

emergency therapeutical management. The treatment should be adjusted to each individual case: anti-thyroid drugs (that may not be always effective), corticosteroid therapy, beta-blockers.

Neuromuscular disorders *(see Adverse Reactions)*
Amiodarone may induce peripheral sensorimotor neuropathy and/or myopathy. Recovery usually occurs with in several months after Amiodarone withdrawal, but may sometimes be incomplete

Eye disorders (see Adverse Reactions)**:**
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.

Pulmonary disorders (see section Adverse Reactions)**:**
Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity such as interstitial pneumonitis. Very rare cases of interstitial pneumonitis have been reported with intravenous amiodarone. A chest X-Ray should be performed when the diagnosis is suspected, in patients developing effort dyspnoea whether isolated, or, associated with deterioration of general health status (fatigue, weight loss, fever). Amiodarone therapy should be re-evaluated since interstitial pneumonitis is generally reversible following early withdrawal of amiodarone (clinical signs usually resolving within 3 to 4 weeks, followed by slower radiological and lung pulmonary function improvement within several months), and corticosteroid therapy should be considered
Very rare cases of severe respiratory complications, sometimes fatal, have been observed usually in the period immediately following surgery (adult acute respiratory distress syndrome); a possible interaction with a high oxygen concentration may be implicated (see Interactions and Adverse Reactions)

Liver disorders (see Adverse Reactions):
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 and within the first 24 hours of IV amiodarone. Therefore, amiodarone dose should be reduced or the treatment discontinued if the transaminases increase exceeds three times the normal range.
Clinical and biological signs of chronic liver disorders due to oral amiodarone may be minimal (hepatomegaly, transaminases increased up to 5 times the normal range) and reversible after treatment withdrawal, however fatal cases have been reported

Severe bullous reactions
Life-threatening or even fatal cutaneous reactions Stevens-Johnson syndrome (SJS), Toxic
Epidermal Necrolysis (TEN) (see section Section “Adverse Reactions”). 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 Interactions):

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

PRECAUTIONS

As undesirable effects *(see Adverse Reactions)* 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 (see Adverse Reactions).

Monitoring *(see Warnings and Adverse Reactions)***:**
Before starting amiodarone, it is recommended to perform an ECG and serum potassium measurement. Monitoring of transaminases *(see Warnings) and* ECG is recommended during treatment.
Moreover, as amiodarone may induce hypothyroidism or hyperthyroidism, particularly in patients with personal history of thyroid disorders, clinical and biological (usTSH) monitoring is recommended before starting amiodarone. This monitoring should be carried out during treatment and for several months following its discontinuation. 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 defibrillation 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 hormone abnormalities *(see Adverse Reactions)***:**
Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T3, free-T4, us TSH) remain interpretable. Amiodarone inhibits peripheral conversion of thyroxine (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.
Hypothyroidism should be suspected if the following clinical signs, usually slight, occur: weight gain, cold intolerance, reduced activity, excessive bradycardia. The diagnosis is supported by a clear increase in serum usTSH. Euthyroidism is usually obtained with in 1 to 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.

Pediatric patients:
The safety and efficacy of amiodarone in paediatrics patients have not been established. Therefore, its use in paediatric patients is not recommended.

Anaesthesia *(see Interactions and Adverse Reactions)***:**
Before surgery, the anaesthetist should be informed that the patient is taking amiodarone.

INTERACTIONS

Pharmacodynamic interactions

- Drugs inducing *Torsade de Pointes* or prolonging QT

-*Drugs inducing Torsade de Pointes*

Combined therapy with drugs that may induce *"torsade de pointes"* is contra – indicated *(see Contraindications)*:
-antiarryhthmic agents such as Class Ia, sotalol, bepridil,
-non-antiarrhythmic agents such as vincamine, some neuroleptics agents, cisapride, erythromycin IV, pentamidine (when parenterally administrated), as there is an increased risk of potentially lethal *"torsade de pointes"*.

- *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 Warnings) and patients should be monitored for QT prolongation.

Fluoroquinolones should be avoided in patients receiving Amiodarone.

- Drugs lowering heart rate or causing automaticity or conduction disorders

Combined therapy with the following drugs is not recommended.
- Beta-blockers and heart rate lowering calcium channel inhibitors (verapamil, diltiazem) as automaticity (excessive bradycardia) and conduction disorders 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* "; other types of laxatives should be used.

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

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

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).

- General anaesthesia (see Precautions and Adverse reactions):

Potentially severe complications have been reported in patients undergoing general anaesthesia: bradycardia (unresponsive to atropine), hypotension, conduction disorders, decreased cardiac output.

Very rare cases of severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal, have been observed usually in the period immediately following surgery. A possible interaction with a high oxygen concentration may be implicated.

EFFECT OF CORDARONE ON OTHER MEDICINAL PRODUCTS

Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP1A1, CYP1A2, CYP3A4, CYP2C9, CYP2D6 and P-glycoprotein and may increase exposure of their substrates.
Due to the long half life of amiodarone, interactions may be observed for several months after discontinuation of amiodarone.

- PgP substrates

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

- *Digitalis:*

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

- ***Dabigatran***

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

- CYP 2C9 substrates

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

- *warfarin*

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

- *Phenytoin*

The combination of phenytoin with amiodarone may 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.

- CYP2D6 substrates

Flecainide :

Amiodarone raises plasma concentrations of flecainide by inhibition of the Cytochrome CYP 2D6. Therefore, flecainide dosage 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:

- **Cyclosporin:** its combination with Amiodarone may increase cyclosporin plasma levels. Dosage should be adjusted.
- **Fentanyl:** its combination with Amiodarone may enhance the pharmacological 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 CYP3A 4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolized by CYP 3 A4 when given with amiodarone.
- **Other drugs metabolized by CYP 3A4:** lidocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, colchicine.

EFFECT OF OTHER PRODUCTS 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 CYP 3A4 inhibitors (e.g grapefruit juice and certain medicinal products) during treatment with amiodarone.

OTHER DRUG INTERACTIONS WITH CORDARONE *(see section Warnings)*
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 *(see section Warnings).*

PREGNANCY

In view of its effects on the fetal thyroid gland, amiodarone is contraindicated during pregnancy, except if the benefits outweigh the risks.

LACTATION

Amiodarone is excreted in breast milk in significant quantities and is therefore contraindicated in breast-feeding mothers.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

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

ADVERSE REACTIONS

The following CIOMS frequency rating is used, when applicable: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).*

Frequency	**Adverse Reaction**
Blood and lymphatic system disorders	
Very rare	Haemolytic anaemia, 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 Warnings and Interactions),* Conduction disturbances (sinoatrial block, AV block of various degrees) *(see Precautions)*
Very Rare	Marked bradycardia or sinus arrest in patients with sinus node dysfunction and / or in elderly patients
Injury, poisoning and procedural complications	
Not Known	Primary graft dysfunction post cardiac transplant (see Section Warning)
Not known	Torsade de pointes *(see Warnings and Interactions)*
Endocrine disorders *(see Warnings and Precautions)*	
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. 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.
Very rare	Optic neuropathy/neuritis that may progress to blindness (see Warnings)
Gastrointestinal disorders	
Very common	Benign gastrointestinal disorders (nausea, vomiting, dysgeusia) usually occurring with loading dosage and resolving with dose reduction
Not known	Pancreatitis/ acute pancreatitis, dry mouth, constipation
General disorders and administration site conditions	
Not known	Granuloma, including bone marrow granuloma
Hepato- biliary disorders (see Warnings and Precautions)	
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	
Not known	Angioneurotic oedema (Quincke's Oedema)
Not known	Anaphylactic/anaphylactoid reaction including shock
Investigations	
Very rare	Increased serum creatinine
Metabolism and nutrition disorders	
Not known	Decreased appetite
Musculoskeletal and Connective Tissue Disorders	
Not Known	Lupus like syndrome
Nervous system disorders	
Common	Extrapyramidal tremor, Nightmares, Sleep disorders
Uncommon	Peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the drug *(see Warnings)*
Very rare	Cerebellar ataxia, Benign intracranial hypertension (pseudo-tumor cerebri), Headache
Not Known	Parkinsonism, parosmia
Psychiatric disorders	
Not Known	Confusional state/delirium, hallucination
Reproductive system and breast disorders	
Very rare	Epididymitis, Impotence
Not Known	Libido decreased
Respiratory, thoracic and mediastinal disorders	
Common	Pulmonary toxicity (alveolar/ interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia/BOOP), sometimes fatal (see Warnings)
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, usually immediately after surgery (possible interaction with a high oxygen concentration (see sections Warnings, Precautions and Interactions)
Skin and subcutaneous tissue disorders	
Very common	Photosensitivity (see Precautions)
Common	Slate grey or bluish pigmentations of the skin 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 diseases	
Very rare	Vasculitis

OVERDOSE

SIGNS AND SYMPTOMS
There is no information available regarding overdosage with intravenous amiodarone.
Not much information is available regarding acute overdose with oral amiodarone. A few cases of sinus bradycardia, heart block, ventricular tachycardia, torsade de pointes, circulatory failure and hepatic injury have been reported.

MANAGEMENT
Treatment should be symptomatic. Neither amiodarone nor its metabolites are removed during dialysis.

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