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

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

Amiodarone Intravenous Infusion I.P.

CORDARONE® 150 mg/3 ml

Active Moiety/Active Ingredient
Amiodarone

Therapeutic or Pharmacological Class
Antiarrhythmics, Class III

Pharmaceutical Form (s)
Ampoules containing 3 mL of solution containing 150 mg of amiodarone

COMPOSITION

Each ampoule contains:
Amiodarone Hydrochloride I.P. 150 mg/3ml solution for IV injection.

THERAPEUTIC INDICATIONS

Serious rhythm disturbances when oral route is not appropriate, namely:
- atrial arrhythmia, with rapid ventricular rhythm;
- Wolff-Parkinson-White syndrome tachycardia;
- Documented symptomatic and incapacitating ventricular arrhythmia.
- Cardiopulmonary resuscitation in the event of cardiac arrest related to ventricular fibrillation resistant to external electric shock.

DOSAGE & ADMINISTRATION

Intravenous infusion
The usual loading dose is 5 mg/kg in 250mL of 5% dextrose solution administered over a period of between 20 to 120 minutes. This may be repeated 2 to 3 times per 24 hour period. The infusion rate should be adjusted to clinical response.

The therapeutic effect appears within the first minutes and then decreases progressively, so a continuous infusion should be set up as a relay.

Maintenance dosage: 10 to 20 mg/kg / 24 hours (usually 600 mg to 800mg and up to 1200 mg / 24 hours) in 250 mL of 5% dextrose solution over several days. The relay to oral administration should be started as soon as the first day of infusion.

Intravenous injection (see Warnings)

Dosage is 5 mg/kg, to be injected over a period of at least 3 minutes. The preparation should not be used along with other preparations in the same syringe.

In the specific case of cardio-pulmonary resuscitation of shock (defibrillator) resistant ventricular fibrillation, a first dose of 300 mg (or 5 mg/kg) amiodarone diluted in 20 mL of 5% dextrose solution is administered via bolus IV injection. An additional 150 mg (or 2.5 mg/kg) IV dose may be considered if the ventricular fibrillation persists.

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 Interactions)
- Thyroid dysfunction
- Known hypersensitivity to iodine or to amiodarone or to any of the excipients
- Pregnancy, unless exceptional circumstances (see Pregnancy)
- Lactation (see Lactation)
- Bi- or tri-fascicular conduction disorders, unless a permanent functioning pacemaker is fitted or, unless the patient is in a special care unit and amiodarone is used under the cover of electrosystolic pacing.
- Severe arterial hypotension, circulatory collapse
- Intravenous injection is contra-indicated in case of hypotension, severe respiratory failure, myocardiopathy or heart failure (possible worsening).

The above contra-indications do not apply when amiodarone is used in the emergency treatment of cardiopulmonary resuscitation of shock (defibrillator) resistant ventricular fibrillation.

WARNINGS

Intravenous injection

- Intravenous injection is generally not advised because of haemodynamic risks (severe hypotension, circulatory collapse); intravenous infusion is preferable whenever possible.
- Intravenous injection is to be done only in emergency where alternative therapies have failed and only in an intensive care unit under continuous monitoring (ECG, blood pressure).
- Dosage is approximately 5 mg/kg body-weight. Except for cases of cardio-pulmonary resuscitation of shock resistant ventricular fibrillation, amiodarone should be injected over a minimum period of 3 minutes. Intravenous injection should not be repeated less than 15 minutes following the first injection even if the latter was only 1 ampoule (possible irreversible collapse).
- Do not mix other preparations in the same syringe. Do not inject other preparations in the same line. If amiodarone should be continued, this should be via intravenous infusion (See Dosage and Administration).

General

Cardiac disorders (See Adverse Reactions):
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 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**.**

Pulmonary disorders (See 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.

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.

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

Intravenous amiodarone should only be used in a special care unit under continuous monitoring (ECG, blood pressure).

To avoid injection site reactions, amiodarone IV should, whenever possible, be administrated through a central venous line (See adverse reactions).

Caution should be exercised in case of hypotension, severe respiratory failure, uncompensated or severe heart failure.

Paediatric patients:

The safety and efficacy of amiodarone in paediatrics patients have not been established. Therefore, its use in paediatric patients is not recommended. Ampoules of injectable amiodarone contain benzyl alcohol (See section composition). There have been reports of fatal 'gasping syndrome' in neonates (children less than one month of age) following the administration of intravenous solutions containing this preservative. Symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardio-vascular collapse.

Anaesthesia (See Interactions)
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%

Blood and lymphatic system disoders
Not Known: Neutropenia, agranulocytosis

Cardiac disorders
Common: Bradycardia, generally moderate
Very rare: Onset or worsening of arrhythmia, sometimes followed by cardiac arrest *(see Warnings and Interactions)*
Very rare: Marked bradycardia, sinus arrest requiring discontinuation of amiodarone, especially in patients with sinus node dysfunction and/or in elderly patients
Not known: Torsade de pointes *(see Warnings and Interactions)*

Injury, poisoning and procedural complications
Not Known: Primary graft dysfunction post cardiac transplant (see Section Warning)

Endocrine disorders
Not Known**:** Hyperthyroidism
Very rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Eye Disorders
Not Known: Optic neuropathy/neuritis that may progress to blindness *(See Section Warnings).*

Gastrointestinal disorders
Very rare: Nausea
Not Known: Pancreatitis/ acute pancreatitis

General disorders and administration site condition
Common: Injection site reactions such as pain, erythema, **edema**, necrosis, extravasation, infiltration, inflammation, induration, thrombophlebitis, phlebitis, cellulitis, infection, pigmentation changes

Hepato-biliary disorders (See Warnings and Precautions)

Very rare: Isolated increase in serum transaminases, which is usually moderate (1.5 to 3 times normal range) at the beginning of therapy. They may return to normal with dose reduction or even spontaneously, Acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, sometimes fatal (see warnings)

Immune system disorders
Very rare: Anaphylactic shock
Not Known: Angioneurotic edema (Quincke's edema)

Musculoskeletal and Connective Tissue Disorders
Not Known: Back pain

Nervous system disorders
Very rare: Benign intra- cranial Hypertension (Pseudo tumor cerebri), Headache
Not Known: Parkinsonism

Psychiatric disorders
Not Known: Confusional state/delirium, hallucination

Reproductive system and breast disorders
Not known: Libido decreased

Respiratory, thoracic and mediastinal disorders
Very rare: Interstitial pneumonitis or fibrosis, sometimes fatal *(see Section warnings),* Severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal (see warnings and interactions), Bronchospasm and/or apnoea in case of severe respiratory failure, and especially in asthmatic patients.

Skin and Subcutaneous tissue disorders
Very rare: Sweating
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
Common: Decrease in blood pressure, usually moderate and transient. Cases of severe hypotension or collapse have been reported following over dosage or a too rapid injection
Very rare: Hot flushes

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.

INCOMPATIBILITIES/ COMPATIBILITIES

The use of medical equipment or devices containing plasticizer such as DEHP (di-2-ethylhexyl phthalate) in presence of amiodarone may result in leaching out of DEHP. In order to minimize patient exposure to DEHP, the final amiodarone dilution for infusion may preferably be administered through non DEHP-containing sets (see Preparation and Handling).

STORAGE CONDITIONS

Ampoules should be stored at room temperature (< 25^{o} C) and protected from light

PREPARATION AND HANDLING

Because of pharmaceutical characteristics, concentrations less than 600 mg/liter should not be used. Only 5% dextrose solution should be used for dilution. Do not mix with other preparations in infusion solution.

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