Cordarone® 150mg/3ml
amiodarone

SANOFI

This product is to be used only by a registered medical practitioner with experience in cardiology

QUALITATIVE AND QUANTITATIVE COMPOSITION

Per ampoule
Amiodarone (INN) hydrochloride.....150mg
Excipients: polysorbate 80, benzyl alcohol, water for injection .....q.s. 3ml

PHARMACEUTICAL FORM

Solution for IV injection in ampoules
Clear pale yellow liquid, practically free from particles.

CLINICAL PARTICULARS

Therapeutic indications

Serious arrhythmias when treatment via the oral route is not appropriate, namely:
- atrial arrhythmia, with rapid ventricular rhythm;
- Wolf-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.

Posology and method of administration

Due to the formulation of the product, do not use concentrations of less than 2 ampoules in 500 ml. Use only isotonic glucose solution.
Do not add any other products to the infusion vehicle.

Amiodarone must be administered via the central venous route except for cardiopulmonary resuscitation in the event of cardiac arrest related to ventricular fibrillation resistant to external electric shock in which case, in the absence of a central venous route, the peripheral venous route may be used (see *Special warnings and special precautions for use*).

Serious arrhythmias when oral use is not suitable, except for cardiopulmonary resuscitation in the event of cardiac arrest related to ventricular fibrillation resistant to external electric shock: Infusion via the central venous route.

- Initial treatment: on average 5 mg/kg in glucose solution, preferably using an electric syringe, administered over 20 minutes to 2 hours, possibly repeated 2 or 3 times per 24-hour period. The short action of the medicinal product requires continuation of the infusion.

- Maintenance treatment: 10 to 20 mg/kg/day (on average 600 to 800 mg/24 h, up to 1.2 g/24 h) in 250 ml glucose solution, over a few days.
  Initiate replacement treatment by the oral route (3 tablets per day), starting from the first day of infusion.

This dosage may be increased to 4 or even 5 tablets per day.

Cardiopulmonary resuscitation of shock-resistant ventricular fibrillation in patients experiencing cardiac arrest.

When administering the medicinal product in this situation, use of a central venous catheter is recommended if immediately available; otherwise, administration may be performed via the peripheral venous route, using the largest possible peripheral vein with the highest possible blood flow.
• The initial intravenous dose is 300 mg (or 5 mg/kg) diluted in 20 ml 5% glucose given as a rapid injection.
• An additional dose of 150 mg (or 2.5 mg/kg) IV may be considered if ventricular fibrillation persists.
• Do not add any other products in the syringe.

Pediatric population
The safety and efficacy of amiodarone in children have not been established.
See *Pharmacodynamic properties* and *Pharmacokinetics properties* for currently available data.
As this medicinal product contain benzyl alcohol, it is contraindicated in premature and full-term infants and in children aged less than 3 years (see *Contraindications* and *Special warnings and precautions for use*).

Contraindications
This medicinal product is contraindicated in the following cases:
- sinus bradycardia and sinoatrial heart block in unpaced patients;
- sinus node disease in unpaced patients (risk of sinus arrest);
- high-degree atrioventricular conduction disorders in unpaced patients;
- hyperthyroidism because of possible exacerbation by amiodarone;
- known hypersensitivity to iodine, amiodarone or to one of the excipients;
- circulatory collapse;
- severe hypotension;
- premature neonates, full-term newborns and children aged less than 3 years, as the medicinal product contains benzyl alcohol;
- 2nd and 3rd trimesters of pregnancy;
- breast-feeding women;
- use in combination with:
  - o torsadogenic medicinal products (excluding antiparasitic drugs, neuroleptics and methadone:
    - class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),
    - class III antiarrhythmics (sotalol, dofetilide, ibutilide),
    - other medicinal products such as: arsenic compounds, bepridil, cisapride, citalopram, escitalopram, diphemanil, dolasetron IV, domperidone, dronedarone, erythromycin IV, levofloxacin, mequitazine, mizolastine, vincamine IV, moxifloxacin, prucalopride, spiramycin IV, toremifene (see *Interaction with other medicinal products and other forms of interaction*).
  - o telaprevie,
  - o cobicistat.

These contraindications do not apply to the use of amiodarone to resuscitate patients experiencing cardiac arrest where a defibrillator has not worked to stop ventricular fibrillation.

Special warnings and special precautions for use
Special warnings

Route of administration

Infusion via the central venous route: serious arrhythmias when treatment via the oral route is not appropriate, except during cardiopulmonary resuscitation of shock-resistant ventricular fibrillation in patients experiencing cardiac arrest
Amiodarone injection must be administered via the central venous route, as administration via the peripheral venous route may lead to injection site reactions, such as local venous irritation.
Amiodarone injection must be used exclusively as an infusion.
Even a very slow direct intravenous injection may exacerbate hypotension, heart failure or severe respiratory failure (see *Undesirable effects*).

Cardiopulmonary resuscitation of shock-resistant ventricular fibrillation in patients experiencing cardiac arrest.
• Administration via the peripheral venous route is generally not recommended due to the hemodynamic risks (severe hypotension, circulatory collapse). The central venous route should be used for infusion whenever possible.
• Use of a central venous catheter is recommended if immediately available; otherwise, administration may be performed via the peripheral venous route, using the largest possible peripheral vein with the highest possible blood flow.
• Supervision in an intensive care unit with continuous monitoring of arterial blood pressure and ECG should be instituted as soon as possible.
• Do not add any other products in the syringe.
• If amiodarone treatment must be pursued, the drug should be administered as an infusion via the central venous route, with continuous monitoring of arterial blood pressure and ECG.

Drug interactions
Concomitant administration of amiodarone with the following medicinal products is not recommended: ciclosporin, diltiazem (by injection) or verapamil (by injection), certain antiparasitic agents (halofantrine, lumefantrine and pentamidine), certain neuroleptics (amisulpride, chlorpromazine, cyamemazine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, pimozide, pipamperone, pipotiazine, sertindole, sulpiride, sultopride, tiapride, zuclopenthixol), fluoroquinolones (other than levofloxacin and moxifloxacin), stimulant laxatives, methadone or fingolimod (see *Interaction with other medicinal products and other forms of interaction).*

Cardiac disorders
• Cases of new arrhythmias or worsening of treated arrhythmias have been reported (see *Undesirable effects*).
• The proarrhythmic effect of amiodarone may occur especially if there are factors that promote QT interval prolongation, such as certain drug combinations and hypokalemia (see *Interaction with other medicinal products and other forms of interaction* and *Undesirable effects*). 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.

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.

Eye disorders
If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed. Appearance of amiodarone-induced optic neuropathy or optic neuritis requires amiodarone withdrawal due to the potential risk of progression to blindness (see Section *Undesirable Effects*).

Severe bradycardia and conduction disorders
Cases of severe, potentially life-threatening bradycardia and conduction disorders have been observed with medicinal products containing sofosbuvir in combination with amiodarone.

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 the initiation of anti-HCV treatment.

Amiodarone should only be used in patients treated with medicinal products containing sofosbuvir in case of intolerance or contraindication to other antiarrhythmics.

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, and following that 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 in the last few months and who are to start treatment with medicinal products containing sofosbuvir.

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

Pulmonary disorders
A few cases of interstitial pneumonitis have been reported with amiodarone injection. The onset of dyspnea or non-productive cough, whether isolated or associated with deterioration of general health status, should suggest pulmonary toxicity, such as interstitial pneumonitis, and requires chest X-ray (see *Undesirable effects*).
Furthermore, some cases of acute respiratory distress syndrome have been observed immediately after surgery in patients treated with amiodarone. Close monitoring of these patients during artificial ventilation is therefore recommended.

Liver disorders
Severe, sometimes fatal, hepatocellular failure may occur within 24 hours following the start of treatment with amiodarone injection. Monitoring of liver function is recommended at the start of treatment, then regularly throughout amiodarone treatment (see *Undesirable effects*).

Excipients
This medicinal product contains 60 mg of benzyl alcohol per 3 ml ampoule. Benzyl alcohol may cause toxic or anaphylactoid reactions in infants and children up to 3 years of age.
Administration of medicinal products containing benzyl alcohol in premature and full-term newborns has been associated with fatal cases of gasping syndrome (symptoms include sudden onset of gasping syndrome, hypotension, bradycardia and cardiovascular collapse).

Precautions for use

- Electrolyte disorders, particularly hypokalemia: it is important to consider any situations in which the patient may be at risk for hypokalemia, as hypokalemia can promote proarrhythmic effects. Hypokalemia should be corrected before initiation of amiodarone therapy.
- Amiodarone injection should only be administered in a specialized hospital setting under continuous monitoring (ECG, BP), except in emergency situations.

Anesthesia

Before surgery, the anesthesiologist should be informed that the patient is on amiodarone. The adverse effects of chronic amiodarone therapy are likely to add to the hemodynamic risk associated with general or local anesthesia. These effects include in particular bradycardia, hypotension, reduced cardiac output and conduction disorders.

Combination of amiodarone (see *Interaction 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 diltiazem should only be considered in the prevention of life-threatening ventricular arrhythmias and during cardiopulmonary resuscitation of shock-resistant ventricular fibrillation in patients experiencing cardiac arrest.

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.

Interaction with other medicinal products and other forms of interaction

Antiarrhythmics

Many antiarrhythmic agents have depressant effects on cardiac automaticity, conduction and contractility.

Combined use of antiarrhythmic agents from different classes can be beneficial, but this therapeutic approach often proves problematic, and requires ECG and close clinical monitoring. Combined use of antiarrhythmic agents which induce torsades de pointes (amiodarone, disopyramide, quinidines, sotalol, etc.) is contraindicated.

Combined use of antiarrhythmic agents from the same class is not recommended, except in exceptional cases, due to the higher risk of adverse cardiac effects.

Use of amiodarone in combination with medicinal products that have negative inotropic properties, that induce bradycardia and/or slow atrioventricular conduction is problematic, and requires clinical and ECG monitoring.

Medicinal products that may induce torsades de pointes

This serious arrhythmia can be induced by a number of medicinal products, regardless of whether they are antiarrhythmics. Hypokalemia (see "Hypokalemic agents") is a predisposing factor, as is bradycardia (see "Bradycardia-inducing agents") and a congenital or acquired pre-existing QT interval prolongation.

These medicinal products include class Ia and III antiarrhythmic agents and certain neuroleptics. For dolasetron, erythromycin, spiramycin, and vincamine, this interaction only occurs with IV forms. In general, using two torsadogenic drugs concomitantly is contraindicated.

However, this does not apply to some of these agents which are considered absolutely

necessary and, instead of being contraindicated, are simply not recommended in combination with other torsadogenic medicinal products. This concerns:
- methadone
- antiparasitic drugs (halofantrine, lumefantrine, pentamidine)
- neuroleptics.

Bradycardia-inducing agents
Numerous medicinal products can induce bradycardia, particularly class Ia antiarrhythmic agents, beta- blockers, some class III antiarrhythmic agents, some calcium antagonists, digitalis drugs, pilocarpine and anticholinesterase agents.

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.

Effect of other medicinal products on amiodarone
CYP3A4 inhibitors and CYP2C8 inhibitors may potentially inhibit amiodarone metabolism and therefore increase exposure.
CYP3A4 inhibitors (e.g. grapefruit juice and certain medicinal products) should preferably not be used during amiodarone treatment.

Contraindicated combinations (see *Contraindication*)

+ Medicinal products that may induce torsades de pointes (apart from antiparasitic agents, neuroleptics and methadone, see "Inadvisable combinations"):o **class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),**
  - o **class III antiarrhythmics (dofetilide, ibutilide, sotalol),**
  - o **other medicinal products, such as: arsenic compounds, bepridil, cisapride, citalopram, escitalopram, diphemanil, dolasetron IV, domperidone, dronedarone, erythromycin IV, levofloxacin, mequitazine, mizolastine, moxifloxacin, prucalopride, spiramycin IV, toremifene, vincamine IV.**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ **Telaprevir**
Cardiac automaticity and conduction disorders with risk of excessive bradycardia.

+ **Cobicistat**
Risk of increased amiodarone-induced adverse effects due to decreased metabolism.

Inadvisable combinations (see *Special warnings and precautions for use*)
+ **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**).
+ **CYP3A4 susbtrates**
Amiodarone is an inhibitor of CYP3A4 and increases plasma concentrations of CYP3A4 substrates, potentially increasing the toxicity of these substrates.

+ **Ciclosporin**
Increased blood ciclosporin concentrations, due to reduced liver metabolism, with a risk of nephrotoxic effects.
Assay of blood ciclosporin concentrations, monitoring of renal function and ciclosporin dose adjustment during amiodarone treatment should be performed.

+ **Diltiazem injection**

Risk of bradycardia and atrioventricular heart block.
If this combination cannot be avoided, close clinical supervision and continuous ECG monitoring should be performed.

+ **Fingolimod**

Potentiation of the bradycardia-inducing effects with potentially fatal outcome. This is particularly true for beta-blockers which inhibit adrenergic compensation mechanisms.
Clinical supervision and continuous ECG monitoring for 24 hours following the first dose should be performed.

+ **Verapamil injection**

Risk of bradycardia and atrioventricular heart block.
If this combination cannot be avoided, close clinical supervision and continuous ECG monitoring should be performed.

+ **Antiparasitics that may induce torsades de pointes (halofantrine, lumefantrine, pentamidine)**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.
Discontinue one of the two treatments, if possible. If the combination cannot be avoided, monitor QT before instituting treatment and monitor ECG.

+ **Neuroleptics that may induce torsades de pointes (amisulpride, chlorpromazine, cyamemazine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, pimozide, pipamperone, pipotiazine, sertindole, sulpiride, sultopride, tiapride, zuclopenthixol).**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ **Methadone**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ **Fluoroquinolones other than levofloxacin and moxifloxacin (contraindicated combinations):**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ **Stimulant laxatives**

Increased risk of ventricular arrhythmias, particularly torsades de pointes (hypokalemia is a predisposing factor).
Correct any hypokalemia before administering the medicinal product and carry out ECG and clinical monitoring, together with electrolyte monitoring.

+ **Fidaxomicine**

Increased plasma fidaxomicine concentrations.

<u>Combinations requiring precautions for use</u>

+ **P-glycoprotein substrates**

Amiodarone is a P-glycoprotein (P-gp) inhibitor. Co-administration with P-gp substrates may lead to increased exposure of these substrates.

+ **Digitalis drugs**

Suppressed automaticity (excessive bradycardia) and atrioventricular conduction disorders.
If digoxin is used, blood digoxin levels can be increased due to reduced digoxin clearance, requiring ECG and clinical monitoring.
If necessary, blood digoxin levels should be monitored and the digoxin dose adjusted.

+ **Dabigatran**

Increase in plasma dabigatran concentrations, with a higher risk of bleeding.
If dabigatran is used postoperatively, clinical monitoring should be performed and, if necessary, the dabigatran dose should be adjusted, without exceeding 150 mg/day.

+ **CYP2C9 substrates**

Amiodarone increases plasma concentrations of CYP2C9 substrates such as vitamin K antagonists and phenytoin.

+ **Vitamin K antagonists**

Increased vitamin K antagonist effect and increased risk of bleeding.
INR should be monitored more frequently. The vitamin K agonist dose should be adjusted during treatment with amiodarone and for 8 days after treatment discontinuation.

+ **Phenytoin (and, by extrapolation, fosphenytoin)**

Increase in plasma phenytoin concentrations with signs of overdose, particularly neurological signs (decreased liver metabolism of phenytoin).
Clinical monitoring and monitoring of plasma phenytoin concentrations should be performed and, if necessary, the phenytoin dose should be adjusted.

+ **CYP2D6 substrates**

• **Flecainide**

Amiodarone increases plasma concentrations of flecainide by inhibiting cytochrome CYP2D6.
The flecainide dose should be adjusted.

+ **CYP3A4 substrates**

Amiodarone is an inhibitor of CYP3A4 and increases plasma concentrations of substrates of this cytochrome, potentially increasing the toxicity of these substrates.

+ **Statins (simvastatin, atorvastatin, lovastatin)**

The risk of muscle toxicity (e.g. rhabdomyolysis) is increased by concomitant administration of amiodarone as statins can be metabolized by CYP3A4. Use of another statin not affected by this type of interaction is recommended.

+ **Other drugs metabolized by CYP3A4 (lidocaine, tacrolimus, sildenafil, midazolam, dihydroergotamine, ergotamine, colchicine, triazolam)**

Amiodarone is an inhibitor of CYP3A4 and increases plasma concentrations of these molecules, potentially increasing the toxicity of these substances.

+ **Lidocaine**

Risk of increased lidocaine plasma concentrations, potentially leading to neurological and cardiac adverse effects, due to decreased liver metabolism by amiodarone.
Clinical and ECG monitoring and, if necessary, monitoring of plasma lidocaine concentrations should be performed. If necessary, the lidocaine dose should be adjusted during treatment and after amiodarone discontinuation.

+ **Tacrolimus**

Increase in blood tacrolimus concentrations due to inhibition of its metabolism by amiodarone.
Assay of blood tacrolimus concentrations, monitoring of renal function and tacrolimus dose adjustment should be performed during combined treatment with amiodarone and after amiodarone discontinuation.

+ **Beta-blockers (other than esmolol and sotalol)**

Automaticity and conduction disorders (suppression of sympathetic compensation mechanisms). ECG and clinical monitoring should be performed.

+ **Beta-blockers in heart failure (bisoprolol, carvedilol, metoprolol, nebivolol)**

Automaticity and cardiac conduction disorders with risk of excessive bradycardia.
Increased risk of ventricular arrhythmias, particularly torsades de pointes. Regular clinical and ECG monitoring should be performed.

+ **Esmolol**

Contractility, automaticity and conduction disorders (suppressed compensatory sympathetic mechanisms).
ECG and clinical monitoring should be performed.

+ **Oral diltiazem**

Risk of bradycardia or atrioventricular heart block, particularly in the elderly. ECG and clinical monitoring should be performed.

+ **Oral verapamil**

Risk of bradycardia or atrioventricular heart block, particularly in the elderly. ECG and clinical monitoring should be performed.

+ **Some macrolides (azithromycin, clarithromycin, roxithromycin)**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

ECG and clinical monitoring should be performed during combined treatment with amiodarone.

+ **Hypokalemic agents: hypokalemic diuretics (alone or in combination), amphotericin B (IV route), glucocorticoids (systemic route), tetracosactide**

Increased risk of ventricular arrhythmias, particularly torsades de pointes (hypokalemia is a predisposing factor).
Correct any hypokalemia before administering the medicinal product and carry out ECG and clinical monitoring, together with electrolyte monitoring.

+ **Bradycardic agents**

Increased risk of ventricular arrhythmias, particularly torsades de pointes. ECG and clinical monitoring should be performed.

+ **Orlistat**

Risk of decreased plasma concentrations of amiodarone and its active metabolite. Clinical monitoring and, if necessary, ECG monitoring should be performed.

+ **Tamsulosin**

Risk of increased tamsulosin-induced adverse effects due to inbibition of its hepatic metabolism.
Clinical monitoring should be performed and the tamsulosin dose adjusted during treatment with the enzyme inhibitor and after its discontinuation, if necessary.

+ **Voriconazole**

Increased risk of ventricular arrhythmias, particularly torsades de pointes, as amiodarone metabolism may be decreased.
Clinical and ECG monitoring should be performed and the amiodarone dose adjusted if necessary.

Combinations to be taken into account

+ **Pilocarpine**

Risk of excessive bradycardia (cumulative bradycardia-inducing effects).

Fertility, pregnancy and lactation

Pregnancy
Animal studies have not demonstrated any teratogenic effects, therefore no malformative effects are expected in humans. To date, substances causing malformations in humans have been shown to be teratogenic in animals during well-conducted studies in two species.
There are not currently enough relevant clinical data to evaluate a possible teratogenic effect of amiodarone when administered during the first trimester of pregnancy.
Since the fetal thyroid gland begins to bind iodine from week 14 of amenorrhea, no effects on the fetal thyroid gland are expected if the drug has been administered before then.
Iodine overload with use of amiodarone beyond this period may cause fetal hypothyroidism which can be seen in laboratory tests or can even manifest clinically as goiter.
Consequently, use of this medicinal product is contraindicated from the 2nd trimester of pregnancy. As benzyl alcohol crosses the placental barrier, solutions for injection should be used with caution in pregnant women.

Lactation
Amiodarone and its metabolite, together with iodine, are excreted in breast milk at concentrations higher than those in maternal plasma. Due to the risk of hypothyroidism in the infant, breast-feeding is contraindicated during treatment with this medicinal product.

Undesirable effects
The adverse effects are presented by system organ class and according to frequency, as follows:

Very common (≥10%); common (≥ 1%, < 10%); uncommon (≥ 0.1%, < 1%); rare (≥ 0.01%, < 0.1%); very rare (< 0.01%); not known (cannot be estimated from the available data).

Cardiac disorders:
Common:
Bradycardia.

Very rare:
Marked bradycardia and, more exceptionally, sinus arrest, reported in certain cases, particular in elderly patients, proarrhythmic effect.

Not known:
Torsades de pointes (see *Special warnings and precautions for use* and *Interaction with other medicinal products and other forms of interaction*)

Gastrointestinal disorders:
Very common:
Nausea.

Not known:
Pancreatitis/acute pancreatitis.

General disorders and administration site conditions:
Common:

Possible inflammatory reaction, such as local venous irritation when administered directly in a peripheral vein, reactions at the injection site, such as pain, erythema, edema, necrosis, extravasation, infiltration, inflammation, phlebitis and cellulitis.

Hepato-biliary disorders:
Cases of liver damage, diagnosed based on elevated serum transaminases, have been reported, as follows:

Very rare:
Generally moderate, isolated elevation in transaminases (1.5 to 3 times normal range) resolving after dose reduction, or even spontaneously;
Acute liver damage with high serum transaminases and/or jaundice, sometimes with fatal outcome, requiring treatment discontinuation.
Chronic liver damage during prolonged treatment (via the oral route). Histological findings are consistent with pseudoalcoholic hepatitis. Given the discreet nature of the clinical and laboratory evidence (inconstant hepatomegaly, elevated serum transaminases between 1.5 and 5 times normal range) regular monitoring of liver function is justified. The diagnosis of chronic hepatic damage should be considered if an elevation, even moderate, in blood transaminases, occurs after more than 6 months of treatment. Clinical disorders and abnormal laboratory values usually resolve after treatment discontinuation,
although in a few reported cases, the course was irreversible.

Immune system disorders:
Very rare:
Anaphylactic shock.

Not known
Cases of angioedema and/or urticaria have been reported.

Endocrine disorders:
Very common:
Thyroid disorders: In the absence of any clinical evidence of thyroid dysfunction, “dissociated” blood thyroid hormone levels (increased T4, normal or slightly lower T3) should not lead to treatment discontinuation.

Common:
Thyroid disorders: Hypothyroidism is typically characterized by signs such as weight gain, sensitivity to cold, apathy, drowsiness; a clear increase in TSH confirms the diagnosis. After treatment discontinuation, normal thyroid function is gradually restored within 1 to 3 months; discontinuation is not mandatory: if amiodarone treatment is necessary, the drug may be continued in combination with thyroid hormone replacement therapy with L-thyroxine, using TSH to determine the dose.
Hyperthyroidism is more misleading, causing only a few symptoms (minor, unexplained weight loss, decreased antianginal and/or antiarrhythmic efficacy), manifesting as psychiatric symptoms in elderly subjects, or even as thyrotoxicosis.
Suppression of ultrasensitive TSH confirms the diagnosis. Amiodarone must be discontinued: this is usually enough to prompt clinical recovery within 3-4 weeks. In serious cases that may be fatal, appropriate treatment should be urgently instituted.
If thyrotoxicosis is a cause for concern, in itself or because of its effect on a precarious myocardial balance, direct corticosteroid therapy (1 mg/kg) over a sufficiently long period (3 months) may be recommended due to the inconsistent efficacy of synthetic antithyroid drugs.
Cases of hyperthyroidism have been reported up to several months after discontinuing amiodarone.

Very rare
Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Nervous system disorders:
Very rare:
Benign intracranial hypertension (pseudotumor cerebri).

Respiratory, thoracic and mediastinal disorders:
Very rare:
Interstitial pneumonitis or fibrosis, sometimes fatal

Acute respiratory distress syndrome, generally associated with interstitial pneumonitis, occasionally with fatal outcome, occurring sometimes immediately after surgery (a possible interaction with high oxygen doses has been suggested). Discontinuation of amiodarone should be considered, as well as the potential benefit of corticosteroid therapy (see *Special warnings and precautions for use*).
Bronchospasm and/or apnea in the event of severe respiratory failure, particularly in asthmatic patients.

Skin and subcutaneous tissue disorders:
Very rare:
Sweating, alopecia.

Not known:
Eczema
Severe, sometimes fatal, cutaneous reactions such as toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome.
Bullous dermatitis
DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms).

Eye disorders
Not known:
Optic neuropathy/neuritis that may progress to blindness.

Vascular disorders:
Common:
Generally moderate and transient fall in blood pressure. Cases of severe hypotension or collapse have been reported, particularly after overdose if the drug is injected too rapidly.

Very rare:
Hot flushes.
Musculoskeletal and connective tissue disorders:
Not known:
Lower back pain, back pain.

Hematological and lymphatic system disorders:
Not known:
Neutropenia, agranulocytosis.

Psychiatric disorders
Not known:
Confusional state, delusion, hallucination.

Reproductive system and breast disorders:

Not known:
Loss of libido.

Injury, poisoning and procedural complications
Not known:
Potentially fatal primary graft dysfunction post cardiac transplant (see *Special warnings and special precautions for use*).

Overdose
No information regarding amiodarone overdose via the IV route is available.
As regards the oral form, acute ingestion of high doses is poorly documented.

A few cases of sinus bradycardia, ventricular arrhythmias, particularly torsades de pointes, and liver damage have been reported. Treatment must be symptomatic. Given the pharmacokinetic profile of the substance, monitoring, particularly of the heart, over a sufficiently long period of time, is recommended.
Amiodarone and its metabolites are not dialyzable.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic class: CLASS III **ANTIARRHYTHMIC -** ATC code: C01BD01.

Antiarrhythmic properties:
- Lengthening of phase 3 of the cardiac action potential without modifying its height or rate of increase (Vaughan Williams class III). This effect, which is isolated, is due to slowing of the potassium channel, with no change in the sodium or calcium channels;
- Bradycardia-inducing effect by reducing sinus automaticity. This effect is not antagonized by atropine;
- Non-competitive alpha and beta-antiadrenergic effect;
- Slowing of sinoatrial, atrial and nodal conduction, which is more pronounced as heart rhythm becomes more rapid;
- No changes in ventricular conduction;
- Prolongation of refractoriness and decreased myocardial excitability in the atria and nodal tissues and ventricles;
- Slowing of conduction and prolongation of refractoriness in the accessory atrioventricular pathways.
- Absence of negative inotropic effects.

Cardiopulmonary resuscitation of shock-resistant ventricular fibrillation in patients experiencing cardiac arrest.

The efficacy and safety of IV amiodarone in patients with out-of-hospital cardiac arrest due to shock- resistant ventricular fibrillation were evaluated in two double-blind studies: the ARREST study, which compared amiodarone with placebo, and the ALIVE study, which compared amiodarone with lidocaine.

The primary endpoint of both studies was the proportion of patients admitted alive to hospital.

• In the ARREST study, 504 patients with out-of-hospital cardiac arrest as a result of ventricular fibrillation, or pulseless ventricular tachycardia refractory to 3 or more defibrillator shocks and epinephrine were randomized to 2 groups and given either 300 mg amiodarone diluted in 20 ml 5%glucose as a rapid injection into a peripheral vein (246 patients) or placebo (258 patients). In the197 patients (39%) who were admitted alive to hospital, amiodarone significantly increased the probability of being resuscitated and admitted to hospital: 44% in

the amiodarone group versus 34% in the placebo group (p = 0.03).

After adjustment for other predictors of outcome, the adjusted odds ratio for survival to hospital admission was 1.6 (95% CI, 1.1 to 2.4; p = 0.02) in the amiodarone group, compared with the placebo group. The incidence of hypotension (59% versus 48%, p = 0.04) or bradycardia (41% versus 25%,p = 0.004) was more common in patients receiving amiodarone than in those given placebo.

• In the ALIVE study, 347 patients with ventricular fibrillation refractory to 3 defibrillator shocks, epinephrine and another defibrillator shock, or with recurrence of ventricular fibrillation after initially successful defibrillation, were randomized to receive either amiodarone (5 mg/kg of estimated body weight, diluted in 30 ml 5% glucose) and a lidocaine placebo, or lidocaine (1.5 mg/kg at a concentration of 10 mg/ml) and an amiodarone placebo containing the same solvent (polysorbate 80). In the 347 patients included in the study, amiodarone significantly increased the probability of being resuscitated and admitted to hospital: 22.8% in the amiodarone group (41 out of 180 patients) versus
12% in the lidocaine group (20 patients of 167), p = 0.009. After adjustment for other factors likely to affect survival, the adjusted odds ratio for survival to hospital admission was 2.49 (95% CI, 1.28 to 4.85; p = 0.007) in the amiodarone group compared with the lidocaine group. There was no difference between the 2 treatment groups in the number of patients requiring management of bradycardia with atropine, or of blood pressure with dopamine, or in the number of patients given lidocaine (in addition to the study medication).

The proportions of patients with asystole after defibrillation and administration of the study medication was significantly higher in the lidocaine group (28.9%) than in the amiodarone group (18.4%), p = 0.04.

Pediatric population:
No controlled clinical studies have been conducted in children. In the published literature, the safety of amiodarone has been studied in 1118 children with various types of arrhythmia.

The following doses were used in pediatric clinical studies:

- loading dose: 5 mg/kg bodyweight over 20 minutes to 2 hours
- maintenance dose: 10 to 15 mg/kg/day over several hours to several days.

If necessary, initiate switch to oral amiodarone therapy at the usual loading dose, starting from the first day of infusion.

Pharmacokinetic properties
After amiodarone injection, plasma decay is very rapid while tissues become impregnated and receptor sites saturated by the drug; peak effects are observed after approximately 15 minutes and decline within 4 hours.
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.

Pediatric population:
No controlled clinical studies have been conducted in children.

Available literature data, which are limited, show no difference in pharmacokinetic parameters between adults and children.

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.

PHARMACEUTICAL PARTICULARS
Incompatibilities and Instruction for use and handling
The use of PVC material or medical devices plasticized with DEHP di(2-ethylhexyl) phthalate can result in the release of DEHP in contact with amiodarone solution for injection. To minimize the patient's exposure to DEHP, it is recommended that the final amiodarone dilution be prepared prior to infusion using equipment that does not contain any DEHP, such as equipment made of DEHP-free PVC, polyolefins (polyethylene, polypropylene) or glass.

Shelf life
Do no use later than the date of expiry.

How supplied
Box of 6 ampoules of 3ml

Storage Condition
Ampoules should be stored below 25°C.

Manufacturer
Sanofi Winthrop Industrie
1, rue de la Vierge - Ambares et Lagrave,
33565 Carbon Blanc Cedex, France.

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