SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CORDARONE 200 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amiodarone hydrochloride ..... 200 mg

For one scored tablet.

Excipient(s) with known effect: Lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Scored tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Prevention of recurrences of:

life-threatening ventricular tachycardias: treatment should be initiated in a hospital setting under monitoring;
documented symptomatic and disabling ventricular tachycardias;
documented supraventricular tachycardias when the need for treatment is established in the case of resistance or contraindication to other treatments;
ventricular fibrillations.

Treatment of supraventricular tachycardias:

Slowing or reduction of atrial fibrillation or atrial flutter.

Amiodarone may be used in the presence of coronary artery disease and/or impaired left ventricular function (see section 5.1).

4.2. Posology and method of administration

Posology

Initial treatment

The usual dosing schedule is 3 tablets per day for 8 to 10 days. In some cases, the initial treatment may have required higher dosages (4 to 5 tablets per day), always over short periods and under electrocardiographic monitoring.

Maintenance treatment

Research the minimum effective dose, which varies by patient, from 1/2 tablet per day (1 tablet every other day) to 2 tablets every day.

Paediatric population

The safety and efficacy of amiodarone in children have not been established. Currently available data are described in sections 5.1 and 5.2.

Method of administration

For oral use.

4.3. Contraindications

This medicinal product is contraindicated in the following situations:

unaided sinus bradycardia and sinoatrial blocks; unaided sick sinus syndrome (risk of sinus arrest);
unaided high-grade atrioventricular conduction disorders; hyperthyroidism due to its possible aggravation by amiodarone;
known hypersensitivity to iodine or amiodarone or any of the excipients; second and third trimesters of pregnancy;
breastfeeding;
in combination with:

- torsadogenic drugs (except antiparasitics, neuroleptics, methadone):
  - class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),
  - class III antiarrhythmics (sotalol, dofetilide, ibutilide),
  - other medicinal products such as: arsenic trioxide, bepridil, cisapride, citalopram, escitalopram, diphemanil, dolasetron IV, domperidone, dronedarone, erythromycin IV, levofloxacin, mequitazine, mizolastine, moxifloxacin, prucalopride, spiramycin IV, toremifene, vincamine IV (see section 4.5)
- telaprevir
- cobicistat.

4.4. Special warnings and precautions for use

Special warnings

Cardiac disorders:

An ECG should be performed prior to treatment initiation. Decreased heart rate may be more pronounced in older patients.

The electrocardiogram was modified on amiodarone. This “cordaronic” modification consists of QT prolongation related to prolonged repolarisation, with the possible development of U waves; this is a sign of therapeutic impregnation and not toxicity.
If a second- or third-degree atrioventricular block, a sinoatrial block or a bifascicular block occurs during treatment, then treatment should be discontinued. A first-degree atrioventricular block must be monitored.
The occurrence of a new rhythm disorder or worsening of a pre-existing, treated rhythm disorder has been reported (see section 4.8).
Such arrhythmogenic effect is possible in particular in the presence of factors promoting the prolongation of the QT interval such as certain medication combinations and/or the existence of hypokalaemia (see sections 4.5 and 4.8). The risk of inducing torsades de pointes with amiodarone appears to be lower with the same degree of interval prolongation than with other antiarrhythmics.

Thyroid manifestations:

The presence of iodine in the molecule falsifies certain thyroid tests (serum protein-bound iodine, PBI); However, a thyroid panel is still possible (T3, T4, TSHus).
Amiodarone may cause thyroid abnormalities, particularly in patients with a history of thyroid disorders. A TSH assay is recommended in all patients before the start of treatment, then regularly during treatment and for several months after discontinuation, and in case of clinical suspicion of dysthyroidism (see section 4.8).

Pulmonary manifestations:

The occurrence of dyspnoea or a dry cough, isolated or associated with altered general condition, should suggest pulmonary toxicity such as interstitial pneumonitis and require radiological monitoring (see section 4.8).

Hepatic manifestations:

Regular monitoring of the liver function is recommended at the start of treatment and then regularly during amiodarone treatment (see section 4.8).

Neuromuscular manifestations:

Amiodarone may cause sensory, motor or mixed peripheral neuropathies and myopathies (see section 4.8).

Ocular manifestations

In case of blurred vision or decreased visual acuity, a complete ophthalmological examination including fundoscopy should be performed

promptly. Discontinuation of amiodarone is required if amiodarone-induced neuropathy or optic neuritis develops due to a potential risk of progression to blindness (see section 4.8)

Severe skin reactions

Skin reactions such as Stevens-Johnson syndrome and Lyell's syndrome (toxic epidermal necrolysis) that can be life-threatening or fatal may occur. If signs or symptoms suggestive of these syndromes appear (such as a progressive skin rash with blisters or mucosal lesions), amiodarone treatment should be discontinued immediately.

Severe bradycardia and conduction disorders

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

Bradycardia generally occurred within hours to days, but cases with a longer time to onset have been observed, mostly up to two weeks after initiation of anti-HCV therapy.

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

If concomitant use of amiodarone is deemed necessary, it is recommended that patients undergo in-hospital cardiac monitoring for the first forty-eight hours of co-administration, after which outpatient monitoring or self-monitoring of the patient's heart rate should be performed daily for at least the first two weeks of treatment.

Due to the long half-life of amiodarone, cardiac monitoring as indicated above should also be performed in patients who have discontinued amiodarone in the past few months and who are to start treatment with medicinal products containing sofosbuvir alone or in combination with other DAAs.

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

Related to amiodarone

The combination (see section 4.5) with:

beta-blockers other than sotalol (contraindicated combination), and esmolol (combination requiring precautions for use),

verapamil and diltiazem,
will only be considered for the prevention of life-threatening ventricular rhythm disorders.

Taking amiodarone is not recommended with ciclosporin, diltiazem (injectable) and verapamil (injectable), certain antiparasitics (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 and fingolimod (see section 4.5).

Linked to the excipients

This medicinal product contains lactose. It is not recommended for use in patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption syndrome (rare hereditary diseases).

Precautions for use

Electrolyte disturbances, especially hypokalaemia: it is important to consider situations that may be associated with hypokalaemia, as hypokalaemia may promote the occurrence of proarrhythmic effects.

- Hypokalaemia will be corrected prior to amiodarone administration.

The adverse effects listed below are most often related to drug overload; They will be avoided, or their importance minimised by carefully researching the minimum maintenance dose.
During treatment, patients are advised not to expose themselves to the sun or to protect themselves from sun exposure.

In children, the tolerance and efficacy of amiodarone have not been assessed in controlled clinical trials. Due to the possible increase in defibrillation threshold and/or pacemaker stimulation of implantable cardiac defibrillators or pacemakers, it is recommended that this threshold be monitored before and several times after initiation of amiodarone therapy as well as during any dose modification.

Anaesthesia

Prior to surgery, the anaesthetist should be informed that the patient is being treated with amiodarone.

Chronic treatment with amiodarone is likely to add, in terms of adverse effects, to the hemodynamic risk of general or local anaesthetics. They concern, in particular, bradycardic and hypotensive effects, decreased cardiac output and conduction disorders.

In addition, a few cases of acute respiratory distress have been observed

immediately following surgical procedures in patients treated with amiodarone. Therefore, close monitoring is recommended during mechanical ventilation of these patients (see section 4.8).

Transplantation

In retrospective studies, the use of amiodarone in transplant recipients prior to heart transplantation was associated with an increased risk of primary graft dysfunction (PGD).

PGD is a life-threatening complication of heart transplantation that manifests as left, right, or biventricular dysfunction occurring within the first twenty-four hours of transplantation and for which there is no identifiable secondary cause (see section 4.8). Serious PGD may be irreversible.

For patients on the heart transplant waiting list, another antiarrhythmic drug should be used as soon as possible before the transplant.

4.5. Interaction with other medicinal products and other forms of interaction

Antiarrhythmic drugs

Many antiarrhythmics may depress automatism, conduction and cardiac contractility.

The combination of antiarrhythmics from different classes may provide a beneficial therapeutic effect but often proves to be very difficult and requires close clinical and ECG monitoring. The combination of antiarrhythmics that cause torsades de pointes (amiodarone, disopyramide, quinidine, sotalol, etc.) is contraindicated.

The combination with antiarrhythmics from the same class is not recommended, except in rare cases, due to the increased risk of adverse cardiac effects.

The combination with drugs with negative inotropic or bradycardic properties, and/or those that slow atrioventricular conduction, is difficult and requires clinical and ECG monitoring.

Medicinal products likely to induce torsades de pointes

This serious cardiac rhythm disorder can be caused by several medicinal products which may or may not be antiarrhythmics. Hypokalaemia (see hypokalaemia-inducing medicinal products) is a predisposing factor, as is bradycardia (see bradycardia-inducing medicinal products) or a pre-existing congenital or acquired QT interval prolongation.

The relevant medicinal products include, in particular, class Ia and III antiarrhythmics and some neuroleptics.

For dolasetron, erythromycin, spiramycin, and vincamine, only the forms administered intravenously are affected by this interaction.

The use of one torsadogenic medicinal product with another torsadogenic medicinal product is contraindicated as a general rule.

However, because of their indispensable nature, some of them are an exception to the rule as they are only not recommended with torsadogenic agents. This is the case with methadone, some antiparasitics (halofantrine, lumefantrine, pentamidine) and some neuroleptics.

Bradycardia drugs

Many medicinal products can cause bradycardia. This is the case, in particular, with class Ia antiarrhythmics, beta-blockers, some class III antiarrhythmics, some calcium channel blockers, digitalis, pilocarpine, anti-cholinesterases, etc.

Effects of amiodarone on other medicinal products

Amiodarone and/or its metabolite, desethylamiodarone, inhibits CYP1A, CYP1A2, CYP3A4, CYP2C9, CYP2D6 and P-glycoprotein, and may increase the exposure of their substrates.

Due to the long duration of action of amiodarone, these interactions may be observed for several months after discontinuation of amiodarone.

Effects of other medicinal products on amiodarone

CYP3A4 and CYP2C8 inhibitors have the potential to inhibit the metabolism of amiodarone and increase its exposure.

It is recommended to avoid CYP3A4 inhibitors (e.g. grapefruit juice and certain medicinal products) during treatment with amiodarone.

Contraindicated combinations

+ Medicinal products likely to cause torsades de pointes (except antiparasitic agents, neuroleptics and methadone, see combinations not recommended),

+ Class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),

+ Class III antiarrhythmics (dofetilide, ibutilide, sotalol),

+ Other medicinal products such as: arsenic trioxide, 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, especially torsades de pointes.

+ Telaprevir

Automatism and cardiac conduction disorders with risk of excessive bradycardia.

+ Cobicistat

Risk of increased side effects of amiodarone due to decreased metabolism.

Combinations not recommended

+ 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 4.4).

+ Substrates of CYP3A4

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

Ciclosporin
Increased ciclosporin blood concentrations, due to decreased hepatic metabolism, with risk of nephrotoxic effects.

Ciclosporin blood concentration assay, control of renal function and ciclosporin dosage adjustment when used during amiodarone treatment.

+ Diltiazem injection

Risk of bradycardia and atrioventricular block.

If this combination cannot be avoided, close clinical and ECG monitoring is required.

+ Fingolimod

Potentiation of bradycardia-inducing effects that may have fatal consequences. Beta-blockers are all the more at risk that they prevent the mechanisms of adrenergic compensation.

Clinical monitoring and continuous ECG for twenty-four hours following the first dose.

+ Verapamil injection

Risk of bradycardia and atrioventricular block.

If this combination cannot be avoided, close clinical and ECG monitoring is required.

+ Antiparasitic agents which are likely to induce torsades de pointes (halofantrine, lumefantrine, pentamidine)

Increased risk of ventricular arrhythmias, especially torsades de pointes.

If possible, one of the two treatments should be discontinued. If the combination cannot be avoided, a prior control of the QT and ECG monitoring should be performed.

+ Neuroleptics likely to cause torsades de pointes (amisulpride, chlorpromazine, cyamemazine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, pimozide, pipamperone, pipotiazine, sertindole, sulpiride, sultopride, tiapride, zuclopenthixol).

Increased risk of ventricular arrhythmias, especially torsades de pointes.

+ Methadone

Increased risk of ventricular arrhythmias, especially torsades de pointes.

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

Increased risk of ventricular arrhythmias, especially torsades de pointes.

+ Stimulant laxatives

Increased risk of ventricular rhythm disorders, particularly torsades de pointes (hypokalaemia is a contributing factor).

Any hypokalaemia should be corrected before the product is administered and clinical, electrolyte, and electrocardiographic monitoring should be performed.

+ Fidaxomicin

Increased plasma concentrations of fidaxomicin.

Combinations that should be used with caution

+ P-gp substrates

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

+ Cardiac glycosides

Depression of automatism (excessive bradycardia) and atrioventricular conduction disorders. If digoxin is used, increase in serum digoxin levels by decreasing digoxin clearance.
Clinical and ECG monitoring, and if applicable, monitor serum digoxin levels and adjust the digoxin dose.

+ Dabigatran

Increased plasma concentrations of dabigatran, with increased risk of bleeding.

In the post-surgical indication: clinical monitoring and dabigatran dose adjustment, if necessary, not to exceed 150 mg/day.

+ Substrates of CYP2C9

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

+ Vitamin K antagonists

Potentiation of the effect of VKAs and risk of bleeding.

More frequent check of the INR. Adjust the dosage of VKAs during treatment with amiodarone and for eight days after discontinuation.

+ Phenytoin (and fosphenytoin, by extrapolation)

Increased plasma concentrations of phenytoin with signs of overdose, particularly neurological symptoms (decreased hepatic metabolism of phenytoin).

Clinical monitoring, check of the plasma concentrations of phenytoin and possible dose adjustment.

+ Substrates of CYP2D6

Flecainide
Amiodarone increases flecainide plasma concentrations by inhibition of the CYP2D6 cytochrome. The flecainide dose should be adjusted.

+ Substrates of CYP3A4

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

Statins (simvastatin, atorvastatin, lovastatin)
The risk of muscle toxicity (e.g. rhabdomyolysis) is increased when amiodarone is co-administered with statins metabolized by CYP3A4. 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.

+ Beta-blockers (except esmolol and sotalol)

Automatism and conduction disorders (removal of sympathetic compensatory mechanisms). ECG and clinical monitoring.
+ Beta blockers for heart failure (bisoprolol, carvedilol, metoprolol, nebivolol)

Automatism and cardiac conduction disorders with risk of excessive bradycardia.

Increased risk of ventricular arrhythmias, especially torsades de pointes. Regular clinical and ECG monitoring.

+ Esmolol

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

ECG and clinical monitoring

+ Oral diltiazem

Risk of bradycardia or atrioventricular block, particularly in elderly patients. ECG and clinical monitoring.
+ Oral verapamil

Risk of bradycardia or atrioventricular block, particularly in elderly patients. ECG and clinical monitoring.

+ Certain macrolides (azithromycin, clarithromycin, roxithromycin) Increased risk of ventricular arrhythmias, especially torsades de pointes. Clinical and electrocardiographic monitoring during combined treatment.
+ Potassium-lowering agents: potassium-sparing diuretics (alone or combined), amphotericin B (intravenously), glucocorticoids (systemically), tetracosactide

Increased risk of ventricular rhythm disorders, particularly torsades de pointes (hypokalaemia is a contributing factor).

Any hypokalaemia should be corrected before the product is administered and clinical, electrolyte, and electrocardiographic monitoring should be performed.

+ Bradycardia-inducing agents

Increased risk of ventricular arrhythmias, especially torsades de pointes. Clinical and

electrocardiographic monitoring.
+ Orlistat

Risk of decreased plasma concentrations of amiodarone and its active metabolite. Clinical and, if necessary, ECG monitoring.
+ Tamsulosin

Risk of increased adverse effects of tamsulosin, by inhibiting its hepatic metabolism.

Clinical monitoring and adjustment of the dosage of tamsulosin during treatment with the enzyme inhibitor and after its discontinuation, if applicable.

+ Voriconazole

Increased risk of ventricular rhythm disorders, particularly torsades de pointes, from possible metabolic impairment from amiodarone.

Clinical and ECG monitoring and possible adjustment of the amiodarone dosage.

Combinations to be considered

+ Pilocarpine

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

4.6. Fertility, pregnancy and lactation

Pregnancy

Animal studies have not demonstrated any teratogenic effect. As there was no teratogenic effect in animals, no malformation is expected in humans. In fact, to date, the substances responsible for malformations in humans were found to be teratogenic in animals during studies performed on two species.

There is currently insufficient pertinent clinical data to assess whether amiodarone has any malformative or foetotoxic effect when it is administered during the first trimester of pregnancy.

Since the foetal thyroid begins to bind iodine from fourteen weeks of amenorrhoea, no impact on foetal thyroid is expected in the event of prior administration.

Iodine overload with the use of this product in the past can lead to biological or even clinical foetal hypothyroidism (goitre).

Therefore, the use of this medicinal product is contraindicated from the second trimester onwards.

Breast-feeding

Amiodarone and its metabolite, as well as iodine, are excreted in milk at higher concentrations than maternal plasma. Because of the risk of hypothyroidism in infants, breast-feeding is contraindicated when this medicinal product is used.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Undesirable effects were classified by system organ class and frequency using the following convention:

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

Eye disorders:

Very common:

Corneal micro-deposits, almost constant in adults, usually remaining localised in the area under the pupil and not contraindicating continued treatment. Exceptionally, they may be accompanied by the perception of coloured halos in dazzling light or blurred vision.

Corneal micro-deposits consist of complex lipid deposits and are reversible following therapy cessation.

Very rare:

Optic neuropathies (optic neuritis) with blurred vision and decreased vision and papilloedema at the back of the eye. The progression may be towards a more or less severe reduction in visual acuity. The relationship to amiodarone does not currently seem to be established. However, in the absence of another clear aetiology, suspending treatment is recommended.

Skin and subcutaneous tissue disorders:

Very common:

Photosensitisation. Exposure to sunlight is not recommended (and, in general, ultraviolet light) during treatment.

Common:

Slate grey or bluish skin pigmentations, in case of prolonged treatment with high daily dosages; such pigmentations slowly disappear following therapy cessation (10 to 24 months).

Very rare:

Erythema during the course
of radiotherapy, Skin rashes,
usually non-specific,
Exfoliative dermatitis, without a clearly established
relationship to the product, Alopecia.

Not known:

Eczema,
Severe skin reactions, sometimes fatal, including toxic epidermal
necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome,
Bullous dermatitis,
DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms).

Endocrine disorders:

Thyroid manifestations

Very common:

Apart from any clinical signs of dysthyroidism, “dissociated” thyroid hormone levels (increase in T4, normal or slightly lowered T3) do not justify therapy cessation.

Common:

Hypothyroidism takes a classic form: weight gain, cold sensitivity, apathy, somnolence; the clear increase in TSH indicates the diagnosis. Discontinuation of administration leads to a gradual return to euthyroidism within one to three months; This discontinuation is not imperative: if justified by the indication, amiodarone can be continued by combining L-thyroxine-based replacement opotherapy, with the TSH being a dosage guide.

Hyperthyroidism is more misleading: pauci-symptomatic (slight, unexplained weight loss, attenuation of antianginal and/or antiarrhythmic efficacy); psychiatric forms in elderly subjects, or even thyrotoxicosis.

The decrease of high-sensitivity TSH makes it possible to confirm the diagnosis. Discontinuing amiodarone is imperative: It is usually enough to initiate clinical recovery within three to four weeks. Serious cases that can lead to the death of the patient require urgent initiation of appropriate treatment.

When thyrotoxicosis is a concern, in itself or because of its impact on a precarious myocardial balance, the changeable efficacy of synthetic antithyroid drugs leads to the recommendation of straightforward (1 mg/kg) and sufficiently prolonged (3 months) corticosteroid therapy. Cases of hyperthyroidism have been reported up to several months after discontinuation of amiodarone.

Other endocrine disorders

Very rare cases of SIADH (inappropriate antidiuretic hormone secretion), particularly when combined with medicinal products that may induce hyponatraemia. See also the “investigations” section.

Respiratory, thoracic and mediastinal disorders:

Common:

Cases of interstitial pneumonitis or diffuse alveolar lung disease and bronchiolitis obliterans organising pneumonia (BOOP), which may be fatal, have been reported. The onset of exertional dyspnoea or a dry cough, either isolated or associated with an altered general condition (fatigue, weight loss, febricula) requires radiological monitoring and, if applicable, therapy cessation. These pneumopathies can progress to pulmonary fibrosis.

Early discontinuation of amiodarone, with or without corticosteroid therapy, leads to the regression of the disorders. The clinical signs usually disappear within three to four weeks; the radiological and functional improvement is slower (several months).

A few cases of pleurisy, usually associated with interstitial pneumonitis, have been reported.

Very rare:

Bronchospasm, especially in asthmatic patients.
Acute respiratory distress syndromes, sometimes fatal, sometimes immediately after a surgical procedure (a possible interaction with high doses of oxygen has been suggested) (see section 4.4).

Not known (cannot be estimated from the available data):

Cases of pulmonary haemorrhage sometimes manifested by haemoptysis have been reported. These pulmonary manifestations often appear to be associated with amiodarone pneumopathy.

Nervous system disorders:

Common:

Tremors or other
extrapyramidal symptoms,
Sleep disorders including
nightmares,
Sensory, motor or mixed peripheral neuropathies.

Uncommon:

Myopathies.
Sensory, motor or mixed peripheral neuropathies and myopathies may occur only after a few months of treatment but sometimes after several years of treatment. These are generally reversible upon therapy cessation.

However, this recovery may be incomplete, very slow and may not appear until several months after therapy cessation.

Very rare:

Cerebellar ataxia,
Benign intracranial hypertension, headaches. The onset of isolated headaches requires screening for an underlying pathology.

Not known:

Parkinsonism syndrome, parosmia.

Hepatobiliary disorders

Cases of hepatic damage have been reported; These cases were diagnosed by elevated serum transaminases. Indeed, the following have been reported:

Very common:

Elevated transaminases, isolated and generally moderate (1.5 times to 3 times the normal value) regressing after dose reduction, or even spontaneously.

Common:

Acute hepatic damage with hypertransaminasaemia and/or jaundice, sometimes fatal, requiring therapy cessation.

Very rare:

Chronic hepatic damage during prolonged treatments.

The histology is pseudo-alcoholic hepatitis. The discretion of the clinical and biological presentation (inconsistent hepatomegaly, hypertransaminasaemia between 1.5 and 5 times the normal range) justifies regular monitoring of liver function.

Hypertransaminasaemia, even moderate, occurring after treatment for more than six months should suggest the diagnosis of chronic hepatic damage. Clinical and biological disorders usually resolve after therapy cessation. A few cases of irreversible progression have been reported.

Cardiac disorders

Common:

Bradycardia, generally moderate and dose-related.

Uncommon:

Conduction disorders (sinoatrial blocks, atrioventricular blocks of various degrees).

Very rare:

Marked bradycardia, exceptionally sinus arrest reported in some cases

(sinus node dysfunction, elderly patients).

Not known:

Torsades de pointes (see sections 4.4 and 4.5).

Gastrointestinal disorders

Very common:

Benign gastrointestinal disorders (nausea, vomiting, dysgeusia) usually occurring from initial treatment and resolving with dose reduction.

Not known:

Pancreatitis/acute pancreatitis, dry mouth, constipation

Reproductive system and breast disorders

Very rare:

Epididymitis. The relationship to the product has not been established.

Vascular disorders

Very rare:

Vasculitis.

Investigations

Rare:

Rare hyponatraemia that may suggest SIADH.

Very rare:

Renal involvement with moderate elevation of creatinine.

Blood and lymphatic system disorders

Very rare:

Thrombocytopenia, haemolytic anaemia, aplastic anaemia.

Not known:

Neutropenia,
agranulocytosis.

Immune system disorders *Not known*:

Cases of angioedema and/or urticaria have been reported. Anaphylactic/anaphylactoid reaction, including shock.

General disorders

Not known:

Granuloma, including bone marrow granuloma.

Metabolism and nutrition disorders

Not known:

Decreased
appetite

Psychiatric disorders

Common:

Libido decreased.

Not known:

Confusional state, delirium, hallucination.

Musculoskeletal and connective tissue disorders:

Not known

Lupus syndrome.

Injury, poisoning, and procedural complications

Not known:

Primary graft dysfunction, potentially fatal after heart transplantation (see section 4.4).

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 reactions via Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9. Overdose

Little information is available regarding acute overdose with amiodarone. Few cases of sinus bradycardia, ventricular rhythm disorder, mainly torsades de pointes and hepatic damage have been reported. The treatment should be symptomatic. Due to the kinetics of the product, adequate and prolonged surveillance, particularly cardiac, is recommended.

Neither amiodarone nor its metabolites are dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ANTIARRHYTHMIC, CLASS III, ATC code: C01BD01.

Antiarrhythmic properties

prolongation of phase 3 of the action potential of the cardiac fibre essentially resulting from a decrease in potassium current (Vaughan Williams class III);
bradycardic effect by decreasing sinus automatism. This effect is not antagonized by atropine; non-competitive alpha- and beta-adrenergic antagonist properties;
slowing of sinoatrial, atrial and nodal conduction, more marked as the rhythm is faster; no change in intraventricular conduction;
increase in refractory periods and decrease in myocardial excitability at the atrial, nodal and ventricular levels;
slowed conduction and prolonged refractory periods in the atrioventricular accessory pathways.

Other properties

decrease in oxygen consumption by moderate fall in peripheral resistance and decrease in heart rate; increase in coronary output by direct effect on the smooth musculature of the myocardial arteries and
maintenance of cardiac output by reduction in pressure and peripheral resistances and absence of negative inotropic effect.

A meta-analysis comprising thirteen prospective randomized controlled studies, including 6,553 patients with a recent myocardial infarction (78%) or chronic heart failure (22%), was conducted.

The mean follow-up of patients ranged from 0.4 to 2.5 years. The daily maintenance dose ranged from 200 to 400 mg on average.

This meta-analysis showed a significant reduction in favour of amiodarone, of 13% of the total mortality (CI 95% 0.78 - 0.99; P = 0.030) and of 29% of the rhythmic mortality (CI 95% 0.59 - 0.85; P = 0.0003).

However, these results must be interpreted with caution considering the heterogeneity of the studies included (heterogeneity mainly related to the selected population, the duration of follow-ups, the methodology used and the results of the studies).

The treatment discontinuation percentage was higher in the amiodarone group (41%) than in the placebo group (27%).

Seven percent of patients on amiodarone had hypothyroidism versus 1% in the placebo group. Hyperthyroidism was detected in 1.4% of patients on

amiodarone versus 0.5% in the placebo group.

Interstitial pneumonitis occurred in 1.6% of patients on amiodarone versus 0.5% in the placebo group.

Paediatric population

No controlled clinical studies have been performed in children. In published studies, the tolerability of amiodarone was assessed in 1,118 children with various arrhythmias.

In paediatric clinical trials, the following doses were used:

Initial treatment: 10 to 20 mg/kg/day for 7 to 10 days (or 500 mg/m2/day if the dose is expressed as body surface area)
maintenance treatment: the minimum effective dose should be used; depending on the individual response, it may vary between 5 and 10 mg/kg/day (or 250 mg/m2/day if the dose is expressed as body surface area).

5.2. Pharmacokinetic properties

Amiodarone is a molecule with slow transit and high tissue affinity.

Its oral bioavailability varies by individual from 30 to 80% (mean value 50%). After one dose, peak plasma concentrations are reached within 3 to 7 hours. Therapeutic activity is obtained, on average, within one week (a few days to two weeks).

The half-life of amiodarone is long with a large inter-patient variability (20 to 100 days). During the first few days of treatment, the product accumulates in most of the body's tissues, particularly in adipose tissue. Elimination appears after a few days and the input/output panel is balanced after a period of one to a few months depending on the individual.

These characteristics justify the use of loading doses to rapidly create the tissue impregnation necessary for therapeutic activity.

Part of the iodine detaches from the molecule and is found in the urine in the form of iodide; it corresponds to 6 mg/24 hours for a daily dose of 200 mg of amiodarone. The rest of the molecule, therefore most of the iodine, is eliminated in the faeces after passing through the liver.

Negligible urinary elimination makes it possible to use the product at the usual doses in patients with renal failure.

After therapy cessation, elimination continues for several months. The persistence of residual activity for ten days to one month must be taken into consideration.

Amiodarone is metabolised mainly by the cytochrome CYP3A4, and also by CYP2C8. Amiodarone and its metabolite, desethylamiodarone, exhibit a potential in vitro to inhibit cytochromes CYP1A1, CYP1A2, CYP2C9,

CYP2C19, CYP2D6, CYP3A4, CYP2A6, CYP2B6 and CYP2C8. Amiodarone and
desethylamiodarone have also a potential to inhibit some transporters such as P-gp and OCT2 (organic cation transporter protein). One study shows a 1.1% increase in concentration of creatinine (an OCT2 substrate).

In vivo data describe amiodarone interactions on CYP3A4, CYP2C9, CYP2D6 and P-gp substrates.

Paediatric population

No controlled clinical studies have been performed in children.

According to the limited and available published data, no difference in pharmacokinetic parameters was noted between adults and children.

5.3. Preclinical safety data

In a two-year carcinogenicity study in rats, amiodarone caused an increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinically relevant exposures.

Since the results of mutagenicity studies were negative, the assumption of an epigenetic rather than genotoxic mechanism is proposed to explain this type of tumour induction.

In mice, if carcinomas were not observed, a dose-dependent thyroid follicular hyperplasia was nevertheless seen. These effects on the thyroid in rats and mice are most likely due to effects of amiodarone on the synthesis and/or release of thyroid gland hormones. The relevance of these findings to humans is low.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose, corn starch, povidone, colloidal anhydrous silica, magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at a temperature not exceeding 30°C.

6.5. Nature and contents of container

30 tablets in blisters (PVC-Aluminium). 50 tablets in blisters (PVC-Aluminium). 100 tablets in blisters (PVC-Aluminium).

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

SANOFI WINTHROP INDUSTRIE
82 AVENUE RASPAIL
94250 GENTILLY

8. MARKETING AUTHORISATION NUMBER

H1991/4102/R1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/02/2026

10. DATE OF REVISION OF THE TEXT

22/08/2026