

1 NAME OF THE MEDICINE

Amiodarone hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amiodarone hydrochloride is a Class III antiarrhythmic agent.

Aratac 100 and Aratac 200 tablets contain 100 mg and 200 mg amiodarone hydrochloride, as the active ingredient, respectively.

List of excipients with known effect:

Aratac also contains sulfites and sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Aratac 100: White, marked "AM" breakline "100" on one side and "G" on other.

Aratac 200: White, marked "AM" breakline "200" on one side and "G" on other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Severe cases of tachyarrhythmias (e.g. Wolff-Parkinson-White syndrome; supraventricular, nodal and ventricular tachycardias; atrial flutter and fibrillation; ventricular fibrillation) not responding to other therapy.

Treatment should be initiated in hospital. It is recommended that the patient should be regularly monitored for possible toxicity (e.g. thyroid function, chest X-ray, ophthalmological examination, liver function etc.) during the entire course of therapy and for several months after discontinuation.

4.2 DOSE AND METHOD OF ADMINISTRATION

Due to poor absorption and wide inter-patient variability of absorption, the initial loading and subsequent maintenance dosage schedules of the drug in clinical use has to be individually titrated. It is particularly important that the minimum effective dose be used. In all cases the patient's management must be judged on the individual response and well being. The following dosage regimen is usually effective.

Adults

Initial Stabilisation. Treatment should be started with 200 mg three times daily and may be continued for 1 week. The dosage should then be reduced to 200 mg twice daily for a further week.

Maintenance. After the initial period the dosage should be reduced to 200 mg daily, or less if appropriate. Rarely, the patient may require a higher maintenance dose. The scored 100 mg tablet should be used to titrate the minimum dosage required to maintain control of the arrhythmia. The maintenance dose should be regularly reviewed, especially where this exceeds 200 mg daily.

Use in Elderly

As with all patients, it is important that the minimum effective dose is used. Whilst there is no evidence that dosage requirements are different for this group of patients, they may be more susceptible to bradycardia and conduction defects if too high a dose is used. Particular attention should be paid to monitoring of thyroid function.

General Considerations

The high initial dose is necessary because of the slow onset of action whilst the necessary tissue levels of amiodarone are achieved. However, excessive dosing during maintenance therapy can cause side effects, some of which are believed to be related to excessive tissue retention of amiodarone. Side effects slowly disappear as the tissue levels fall after the dosage is reduced or the drug withdrawn. If the drug is withdrawn, residual tissue bound amiodarone may persist for 3 to 12 months, but the likelihood of recurrence of cardiac arrhythmias during this period should be a consideration. The important factor is that the patient requires monitoring regularly to ensure that adverse effects are detected early and the dosage adjusted accordingly. It is particularly important that the minimum effective dose be used.

4.3 CONTRAINDICATIONS

- Known hypersensitivity to iodine or amiodarone or to any of the excipients.
- Pregnancy and Lactation (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy, Use in Lactation)
- In patients in whom bradycardia or AV block is sufficient to cause syncope, patients with sick sinus syndrome (risk of sinus arrest) or with severe atrioventricular conduction disorders, Aratac should only be used in conjunction with a pacemaker.
- Sinus bradycardia and sino-atrial heart block.
- Aratac is contraindicated in patients with evidence, or a history, of thyroid dysfunction.
- Combined therapy with drugs which may induce Torsades de Pointes (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
- Hypotension, severe respiratory failure, cardiomyopathy, heart failure, circulatory collapse, severe arterial hypotension and bi- or tri-fascicular conduction disorders.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

It is recommended to perform an ECG and serum potassium measurement before treatment initiation.

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

Thyroid Hormone Abnormalities

As amiodarone may induce thyroid disorders (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)), particularly in patients with personal or family history of thyroid disorders, clinical and biological monitoring [ultrasensitive TSH (usTSH) assay] is recommended before starting treatment, during treatment and for several months following treatment discontinuation. Serum usTSH levels should be measured when thyroid dysfunction is suspected. Severe cases, with clinical presentation of thyrotoxicosis, sometimes fatal, require emergency therapeutic management.

Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T3, free-T4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of thyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum free-T4, free-T3 being slightly decreased or even normal) in clinically euthyroid patients. There is no reason in such cases to discontinue amiodarone treatment.

Hypothyroidism should be suspected if the following clinical signs, usually slight, occur: weight gain, cold intolerance, reduced activity, excessive bradycardia. The diagnosis is supported by a clear increase in serum usTSH. Euthyroidism is usually obtained within 1 to 3 months following the discontinuation of treatment. In life-threatening situations, amiodarone therapy can be continued, in combination with levothyroxine. The dose of levothyroxine is adjusted according to TSH levels.

Hyperthyroidism

Hyperthyroidism may occur during amiodarone treatment, or, up to several months after discontinuation. Clinical features, usually slight, such as weight loss, onset of arrhythmia, angina, and congestive heart failure should alert the physician. The diagnosis is supported by a clear decrease in serum ultrasensitive TSH (usTSH) level, in which case amiodarone should be withdrawn. Recovery usually occurs within a few months following

withdrawal of treatment; clinical recovery precedes the normalisation of thyroid function tests. Severe and sometimes fatal cases, with clinical presentation of thyrotoxicosis, require emergency therapeutical management. The treatment should be adjusted to each individual case: for example anti-thyroid drugs, corticosteroid therapy, beta-blockers.

Neuromuscular disorders

Amiodarone may induce peripheral sensorimotor neuropathy and/or myopathy. Recovery usually occurs within several months after amiodarone withdrawal, but may sometimes be incomplete.

Pacemakers/Implantable Defibrillators

In the context of chronic administration of antiarrhythmic drugs, cases of increase in ventricular defibrillation and/or pacing threshold of pacemakers or implantable cardioverter defibrillator devices have been reported, potentially affecting their efficacy. Therefore, a repeated verification of the functioning of such devices before and during amiodarone treatment is recommended.

Anaesthesia

Before surgery the anaesthetist should be informed that the patient is taking amiodarone.

Cardiac Disorders

The pharmacological action of amiodarone induces ECG changes such as QT prolongation (related to prolonged repolarisation) with the possible development of U-waves.

Aratac is not contraindicated in patients with latent or manifest heart failure, but caution should be exercised as existing heart failure may occasionally be worsened. In such cases amiodarone should be associated with the usual cardiotoxic and diuretic treatment.

Excessive doses may lead to atropine resistant bradycardia and to conduction disturbances, particularly in elderly patients or during digitalis therapy. Amiodarone, like quinidine and disopyramide, has caused atypical ventricular tachycardia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Cardiovascular). In patients with previous history of the above condition, amiodarone should be avoided. Use of higher doses of amiodarone is not advisable in persons with a history of atypical ventricular tachycardia previously induced by another antiarrhythmic agent.

Treatment should be discontinued in case of second or third degree atrioventricular block, sinoatrial block, bifascicular or trifascicular block.

Onsets of new arrhythmias or worsening of treated arrhythmias, sometimes fatal, have been reported. It is important, but difficult, to differentiate a lack of efficacy of the drug from a proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects are more rarely reported with amiodarone than with the other antiarrhythmic agents, and generally occur in the context of drug interactions and/or electrolytic disorders (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone is used in combination with sofosbuvir alone or in combination with another hepatitis C virus (HCV) direct acting antiviral (DAA), such as daclatasvir, simeprevir or ledipasvir. Therefore, co-administration 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 alone or 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 (such as shortness of breath, light-headedness, palpitations and fainting), and should be advised to seek urgent medical advice if they experience them.

Primary graft dysfunction (PGD) post cardiac transplant

In retrospective studies, amiodarone use in the transplant recipient prior to heart transplant has been associated with an increased risk of PGD.

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

ECG Monitoring

Regular ECG monitoring is recommended in patients on long-term therapy with amiodarone. U waves, deformed T waves and QT prolongation (related to prolonged repolarisation) may occur in the ECG because of the fixing of amiodarone in the myocardial tissues, and is not an indication for withdrawing amiodarone.

The prolongation of QT interval occurs in almost all patients, as this is related to the electrophysiological and antiarrhythmic properties of the drug. Prolongation of the actual QT above 0.6 seconds rather than QTC or QRS widening, may be an important warning sign that requires modification of therapy. Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm (atypical ventricular tachycardia; *Torsade de Pointes*), particularly in elderly patients or during digitalis or other antiarrhythmic therapy. In such circumstances amiodarone should be temporarily withdrawn.

Ocular Changes

Corneal deposits develop in almost all patients (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Ocular) and regular ophthalmological monitoring (e.g. slit lamp biomicroscopy, visual acuity, ophthalmoscopy, etc.) is recommended. If blurred or decreased vision occurs, complete ophthalmological examination including fundoscopy should be promptly performed. Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness.

Pulmonary Disorders

Clinical and radiological evidence of pulmonary fibrosis and/or pneumonitis has been reported, sometimes presenting as unexplained or disproportionate dyspnoea (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Respiratory). Regular chest X-ray should be performed routinely in patients undergoing long-term therapy or when diagnosis is suspected. The effect has usually been reversible with corticosteroid therapy and/or reduction or withdrawal of amiodarone therapy.

Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) 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.

Skin Reaction

Photosensitivity is quite common (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Dermatological) and there is a wide spectrum of skin reactions, ranging from an increased propensity to suntan to intense burning and erythema and swelling of the exposed area. The intensity of these reactions could be alleviated by a reduction in dosage or by application of a protective sunscreen. Patients should be instructed to avoid exposure to the sun or use protective measures during therapy.

Some patients have developed skin pigmentation (slate grey/purple colour) of the exposed areas. This pigmentation can be avoided if doses are kept as low as possible. If the pigmentation is cosmetically unsightly, amiodarone should be discontinued if alternative therapy is possible.

If symptoms or signs of Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) (e.g. progressive skin rash often with blisters or mucosal lesions) are present, amiodarone treatment should be discontinued immediately.

Neurological Toxicity

Peripheral neuropathy could occur in patients on long-term high dosage (generally over 400 mg/day) regimen (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Nervous System).

Intracellular inclusion bodies, similar to those seen in skin, have been demonstrated in peripheral nerve fibres. Sensorimotor neuropathy, with a glove and stocking distribution, and myopathy have been reported in patients. Histologically, segmental demyelination of the nerve fibres has also been demonstrated. After discontinuation of the drug, the neurological complication is slowly and incompletely resolved.

Drug Interactions

Concomitant use of amiodarone is not recommended with the following drugs: beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem) or stimulating laxative agents which may cause hypokalaemia. (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

Hepatic Dysfunction

Regular monitoring of liver function tests (transaminases) is recommended as soon as amiodarone is started and during treatment.

Elevation of liver enzyme (e.g. serum aspartate aminotransferase, serum alanine aminotransferase, glutamyl transpeptidase) levels occurs quite commonly in patients undergoing treatment with amiodarone and in some cases are asymptomatic. The changes appear to be dose dependent rather than an idiosyncratic type. Hepatotoxicity has occasionally been reported (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Hepatic) and close monitoring of hepatic function with liver function tests 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. 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 five times the normal range) and reversible after treatment withdrawal; however, fatal cases have been reported.

Use in Hepatic Impairment

Because of the potential risk of hepatotoxicity and/or accumulation, amiodarone should be used with extreme caution in patients with hepatic disease.

Use in Renal Impairment

Renal excretion of the drug is minimal. This suggests that modification of the dose of amiodarone in patients with renal failure is unnecessary.

Use in the Elderly

In the elderly, heart rate may decrease markedly.

Paediatric Use

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

Effects on Laboratory Tests

Thyroid Function Tests

Amiodarone contains 2 atoms of iodine and bears a structural resemblance to the molecule of thyroxine. A 300 mg maintenance dose of amiodarone has been reported to yield 9 mg/day of iodine at steady state, well in excess of the highest normal dietary intake.

As a consequence of taking the drug and in the absence of any clinical thyroid dysfunction, changes in tests of thyroid function may occur, variable in number and degree. Typically, the PBI, iodine uptake, serum thyroxine (T₄), reverse triiodothyronine (rT₃) and free thyroxine index (FTI) rise and serum triiodothyronine (T₃) falls.

Abnormalities, either multiple or single, may occur in approximately 12% of patients. In particular, a low T₃ syndrome has been described, as with other drugs such as dexamethasone.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacodynamic Interactions

Drugs Inducing Torsade de Pointes

Combined therapy with drugs which may induce Torsades de Pointes is contraindicated (see Section 4.3 CONTRAINDICATIONS).

Antiarrhythmic Agents, such as:

- Class IA Antiarrhythmic Agents, including:
 - *Disopyramide*: Combined treatment of amiodarone and disopyramide causes an increase in the QT interval.
 - *Procainamide*: Serum levels of procainamide increase significantly with coadministration of amiodarone and secondary to this increase, cardiac, gastrointestinal and neural toxicity may develop.
 - *Quinidine*: Atypical ventricular tachycardia with QT prolongation may develop after amiodarone is added to a stable quinidine regimen. This is thought to be due to either a change in the protein or receptor binding of quinidine. Serum levels of quinidine can increase significantly with concomitant amiodarone therapy. Careful monitoring of the electrocardiogram for QT interval prolongation and of serum levels of quinidine is indicated when amiodarone is added to quinidine treatment.
- Mexiletine: Co-administration with amiodarone increases QT interval.
- Sotalol.
- Bepridil.

Non-Antiarrhythmic Agents, such as: vincamine, some neuroleptic agents, cisapride, erythromycin IV or pentamidine IV, as there is an increased risk of potentially lethal *Torsades 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 Torsades de Pointes may increase (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) 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-Adrenergic Blocking Drugs: Amiodarone itself exhibits noncompetitive α - and β -adrenergic inhibition. It should be used with caution in patients on beta-blockers as it may potentiate bradycardia and conduction disorders may occur.

- Calcium Antagonists: Co-administration of amiodarone with drugs of the calcium antagonist type may lead to undue bradycardia and conduction disorders may occur.
- MAO Inhibitors: Co-administration with monoamine oxidase inhibitors is contraindicated on theoretical grounds.

Agents Which May Induce Hypokalaemia

Combined therapy with the following drugs is not recommended:

- Stimulating Laxative Agents: Their use may cause hypokalaemia and therefore increase the risk of Torsades de Pointes; other types of laxative agents should be used.

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

- Diuretics inducing hypokalaemia, either alone or combined.
- Systemic corticosteroids (glyco-, mineralo-), tetracosactide (tetracosactrin).
- Amphotericin B (amphotericin) (IV).

It is necessary to prevent the onset of hypokalaemia (and to correct hypokalaemia); the QT interval should be monitored and, in case of ‘torsades de pointes’, antiarrhythmic agents should not be given (ventricular pacing should be initiated; IV magnesium may be used).

General Anaesthesia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS))

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

A few cases of severe respiratory complications, such as adult acute respiratory distress syndrome, sometimes fatal, have been observed most often in the period immediately after surgery. A possible interaction with a high oxygen concentration may be implicated.

Effect of Amiodarone on the Medicinal Products

Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP 1A1, CYP 1A2, CYP 3A4, CYP 2C9, CYP 2D6 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.

P-gp Substrates

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

- Digitalis: Co-administration of amiodarone to patients already receiving digitalis increases plasma digoxin concentrations by about 70%. This is possibly due to the decrease in digoxin clearance and therefore precipitates toxicity and could lead to disturbances in automaticity (severe bradycardia) and conduction disturbances with the appearance of idioventricular rhythm. The mechanism of action is unknown, but amiodarone may displace tissue glycoside or interfere with digoxin excretion. ECG and digoxin plasma levels should be monitored and patients should be observed for clinical signs of digoxin toxicity. It may be necessary to adjust dosage of digoxin 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 and Other Anticoagulant Agents: Amiodarone raises the concentration of warfarin. The combination of warfarin with amiodarone potentiates the effect of the anticoagulant therapy and increases the risk of bleeding. More frequent monitoring of prothrombin (INR) level and dosage adjustment of oral anticoagulant during treatment with and after discontinuation of amiodarone therapy is necessary
- Phenytoin: Amiodarone raises plasma concentrations of phenytoin. The combination of phenytoin and amiodarone may lead to increases in plasma phenytoin levels with signs of overdosage (particularly 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.

CYP 2D6 Substrates

- Flecainide: Amiodarone increases the concentration of flecainide plasma levels through inhibition of the cytochrome CYP 2D6. The dosage of flecainide should be adjusted.

CYP 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.

- Ciclosporin: because of the possible increase of ciclosporin plasma levels related to a decrease of the clearance of this drug, dosage should be adjusted.
- Fentanyl: combination with amiodarone may enhance the pharmacologic effects of fentanyl and increase the risk of its toxicity.
- Statins metabolised by CYP 3A4: The risk of muscular toxicity is increased by concomitant administration of amiodarone with statins metabolised by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolised by CYP 3A4 when given with amiodarone.
- Other drugs metabolised by CYP 3A4: lidocaine (lignocaine), tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, colchicine.

Effect of Other Medicinal Products in Amiodarone

CYP 3A4 inhibitors and CYP 2C8 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.

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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Other consideration should be given to the possibility that amiodarone may alter the plasma concentration of other drugs, particularly those which are highly protein bound.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Not data available.

Use in Pregnancy

Pregnancy Category: C

Because of the long half-life of amiodarone and its major metabolite, and the potential to cause abnormal thyroid function, effects on the foetal thyroid gland and bradycardia in the foetus, its use is probably best

avoided in the three months before and throughout the duration of pregnancy. Amiodarone is contraindicated in pregnancy. When exposure of the foetus is unavoidable, thyroid function (including TSH) should be assessed promptly in the newborn infant.

No teratogenic effects have been observed in animals. The drug does cross the placenta. In one study a 35 year old woman administered amiodarone in the last weeks of pregnancy, transplacental passage of amiodarone and desethylamiodarone was found to be 10% and 25% respectively. Changes in maternal thyroid function were similar to those seen in other patients receiving amiodarone therapy (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Endocrine) but there was no evidence of clinical hyperthyroidism. The baby's TSH level on day 4 was normal and it had no goitre and was clinically euthyroid. However, the authors caution the use of amiodarone in pregnancy or in those likely to conceive whilst on amiodarone therapy. The long half-life of the drug requires that the drug be stopped several months before conception. The possible adverse effects of amiodarone on the foetal thyroid are of concern since administration of iodine (of which there are 75 mg in a 200 mg dose of amiodarone) during pregnancy may cause foetal goitre, hypothyroidism and mental retardation.

Another patient received 800 mg amiodarone for 1 week (maintenance dose thereafter was 400 mg daily) in her 34th week of pregnancy. Neonatal levels of amiodarone were 25% of the maternal level. Although the infant's liver and thyroid function tests were normal, it was bradycardic during labour and for the first 48 hours after birth.

Use in Lactation

As amiodarone and its desethyl metabolite are secreted in breast milk and its safety in the newborn has not been established, it should not be given to nursing mothers. Amiodarone is contraindicated in breast-feeding mothers. If a situation demands that amiodarone be given to a nursing mother, alternative infant feeding should be instituted.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Amiodarone has been reported to cause frequent and potentially serious toxicity. The incidence, variety and severity of the effects varied from study to study. Most of the adverse effects are also related to dosage and duration of amiodarone, concurrent use of other antiarrhythmic agents, severity of the underlying disease state, and individual variation in the pharmacokinetic profile of the drug.

More Common Reactions

Biochemical Abnormalities

Abnormal liver function tests (increased AST, ALT and alkaline phosphatase) have been reported.

Abnormal thyroid function tests (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Effects on Laboratory Tests)

Cardiovascular

Atypical ventricular tachycardia (*Torsade de Pointes*): Amiodarone-induced atypical ventricular tachycardia has been described. Earlier reports describe combination therapy in which other drugs, or clinical situations, could have been implicated. However, in 2 patients given disopyramide and amiodarone, on withdrawal of the amiodarone, the disopyramide did not induce atypical ventricular tachycardia.

Bradycardia: Marked bradycardia or sinus arrest has occasionally been reported in patients with sinus node dysfunction or elderly patients. Reports of moderate and dose related bradycardia are common.

Cardiac Failure: Exacerbation of cardiac failure has been reported rarely.

Other: Sinus arrest and intrahisian block have been reported.

Dermatological

Photosensitivity commonly occurs in patients on amiodarone therapy. This can usually be alleviated by the use of topical sunscreen and other protective measures.

Less frequently, bluish skin discolouration and slate grey facial pigmentation have been reported. These adverse effects are partially dependent on dose and duration of treatment. Erythema during the course of radiotherapy, facial flushing and hair loss have been reported.

Skin rashes, usually non-specific, including exceptional cases of exfoliative dermatitis have been reported; the relationship with the drug has not been formally established.

Gastrointestinal

Nausea, vomiting, anorexia, constipation and dysgeusia have been reported.

Endocrine

Effects on the Thyroid

Both hyper- and hypothyroidism have occurred during or soon after treatment with amiodarone. Simple monitoring of the usual biochemical tests is confusing because some (PBI and ^{131}I uptake) are invalidated and others (T_4 , T_3 and FTI) may be altered where the patient is clearly euthyroid. Clinical monitoring is therefore recommended before starting treatment, during treatment and should be continued for some months after discontinuation of amiodarone treatment. Serum TSH levels should be measured when thyroid dysfunction is suspected.

The signs of thyroid hyperactivity to be sought are weight loss, asthenia, restlessness, a recurrence of cardiac dysrhythmia, onset of angina or congestive heart failure. The diagnosis may be confirmed by the finding of an elevated serum triiodothyronine (T_3), a low level of thyroid stimulating hormone, (TSH) and a reduced TSH response to thyrotrophin releasing hormone (TRH). (Elevation of reverse triiodothyronine (rT_3) may also be found).

Hyperthyroidism occurring during amiodarone therapy could be serious and sometimes fatal due to coexistence of ischaemic heart disease and/or life-threatening arrhythmias in most of the patients. The risk of developing hyperthyroidism persists for at least 3 months after discontinuation of treatment. Patients who receive amiodarone should be instructed to consult their physician in the event of exacerbation of angina or recurrence of tachycardia after successful therapeutic response, even when such untoward episodes occur up to 6 months after the drug is discontinued.

The clinical features of hypothyroidism, such as weight gain and reduced activity and/or excessive bradycardia with regard to the expected effect of amiodarone should alert the physician. The onset may be abrupt. The diagnosis may be supported by the presence of an elevated serum TSH level and an exaggerated TSH response to TRH . The thyroxine (T_4), T_3 , and free thyroxine index (FTI) may be low.

Courses of antithyroid drugs have been used for the treatment of thyroid hyperactivity; large doses may be required initially.

Thyroid hypofunction may be treated cautiously with levothyroxine.

Other:

Weight gain has occasionally been reported.

Hepatic

Elevations of liver enzymes may occur from time to time during therapy and are usually transient or respond to a reduction in dosage. Isolated elevation of serum transaminases, which are usually moderate have been reported at the beginning of therapy. They may regress with dose reduction or even spontaneously.

A few cases of acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, have also been reported; in such cases treatment should be discontinued, which in most cases results in normalisation of liver function tests. However, some cases of death related to acute liver disorders have infrequently been reported.

There have also been reports of chronic liver disease (pseudo alcoholic hepatitis, cirrhosis), sometimes fatal. Clinical signs and biological changes may be minimal (possible hepatomegaly, transaminases elevated 1.5 to 5 times normal). Regular monitoring of liver function is therefore recommended during therapy. Clinical and biological abnormalities usually regress when treatment is stopped, but fatal cases have been reported.

Nervous System

CNS effects include tremor, insomnia, headaches, dizziness, vertigo, fatigue, sleep disorders, vivid dreams, nightmares, paraesthesia, gait abnormalities, and abnormal nerve conduction.

Extrapyramidal symptoms appeared in 2 of 51 (4%) patients taking 800 mg/day of amiodarone for 4 to 18 months, and in one patient given 100 mg/day for 5 to 6 days respectively.

Uncommon reports of peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the drug, have been received. Several cases of neuropathy indicating amiodarone-induced neuropathy have been reported. In two studies electron microscope findings are detailed. Neuromyopathy has been reported in one patient given alternating doses of 200 to 400 mg/day and peripheral neuropathy in 5 patients taking between 600 and 800 mg/day for periods ranging from 4 to 18 months. Proximal muscle weakness has been described in 4 to 6% of patients with thigh muscle being involved in patients taking high doses (800 mg/day or more).

Ocular

Corneal microdeposits occur in over 90% of patients. In one study microdeposits were present in 30% at 5 to 8 weeks, in 55% at 3 months and in 95% at 9 months. In another study corneal deposits took 8 weeks to develop but were evident in all patients.

Amiodarone keratopathy is related to dosage and duration of treatment. Patients on low doses (100 to 200 mg/day) retain clear corneas or show stage 1 changes (characterised by the coalescence of fine punctate, greyish golden brown opacities into a horizontal linear pattern in the inferior cornea). Those on high doses (400 to 1400 mg/day) develop stage 2 (characterised by additional arborizing and horizontal lines) and stage 3 (characterised by a verticillate, whorl-like pattern) changes which are dependent on duration of treatment. The keratopathy progresses, even with reduced dosage, however, complete regression occurs when the drug is withdrawn. Complete clearing is reported to occur from between 3 and 7 months after withdrawal of the drug.

Corneal microdeposits are essentially benign in nature causing no visual disturbances and have only rarely given rise to symptoms such as visual coloured haloes in dazzling light or blurred vision. Corneal microdeposits consist of complex lipid deposits and are reversible following discontinuation of treatment.

A few cases of neuropathy/optic neuritis have been reported. At present, the relationship to amiodarone has not been formally established. If blurred or decreased vision occurs, ophthalmological 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.

Psychiatric

Chronic anxiety has been reported.

Respiratory

Cases of pulmonary toxicity (alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia/BOOP), sometimes resulting in fatalities have been reported.

Chest X-ray should be performed in patients developing dyspnoea (at effort), or any new respiratory symptom, while taking amiodarone, whether in isolation or associated with deterioration of general health status (fatigue, weight loss, fever).

Pulmonary disorders are generally reversible following early withdrawal of amiodarone therapy. Corticosteroid therapy may also be considered. Clinical signs usually resolve within 3 to 4 weeks, followed by slower radiological and lung function improvement (several months).

A few cases of bronchospasm have been reported in patients with severe respiratory failure and especially in asthmatic patients.

A few cases of adult acute respiratory distress syndrome, sometimes resulting in death, have been observed, usually immediately after surgery (a possible interaction with high oxygen concentration may be implicated).

Less Common Reactions

Cardiovascular

Onset or worsening of arrhythmia, sometimes followed by cardiac arrest.

Conduction disturbances (sinoatrial block, AV block of various degrees).

Marked bradycardia or sinus arrest in patients with sinus node dysfunction and/or in elderly patients.

Cases of torsade de pointes have been reported.

Dermatological

Enhanced pustular psoriasis has been observed.

Alopecia, urticaria and eczema have been reported.

Genitourinary

Worsening of chronic renal failure and one case of symptomatic hypercalcaemia have been reported.

Haematological

There has been a single case of bone marrow depression, but cause and effect was not established.

There have been rare cases of various clinical features which may suggest a hypersensitivity reaction: vasculitis, renal involvement with elevation of creatinine levels, thrombocytopenia.

Very rarely cases of haemolytic anaemia or aplastic anaemia have also been reported.

Neutropenia, agranulocytosis and granuloma, including bone marrow granuloma has been reported.

Immunological

Positive antinuclear antibodies and elevated immunoglobulin level were noted in one patient with amiodarone induced pulmonary fibrosis.

Musculoskeletal and Connective Tissue Disorders

Lupus like syndrome has been reported.

Nervous System

Delay in nerve conduction.

Parkinsonism and parosmia have also been reported.

Ocular

Interference with visual acuity has been rarely observed in association with corneal microdeposits; gritty eyes; blurred vision; itching or burning.

Endocrine

Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Gastrointestinal

Pancreatitis/acute pancreatitis, dry mouth, constipation and decreased appetite have been reported.

Psychiatric Disorders

Confusional state/delirium and hallucination have very occasionally been reported.

Other

There have been reports of epididymitis, epididymo-orchitis, impotence and decreased libido.

Isolated cases of angioneurotic oedema (Quincke's oedema) and pulmonary haemorrhage have been reported. Cerebellar ataxia, benign intracranial hypertension (pseudotumour cerebri) are very rarely reported.

Serious or Life-Threatening Reactions***Cardiovascular***

Bradycardia, conduction disturbances; atypical ventricular tachycardia.

Injury, poisoning and procedural complications

Primary graft dysfunction post cardiac transplant.

Respiratory

Pulmonary fibrosis and/or alveolitis.

Immune System Disorders

Anaphylactic/anaphylactoid reaction including shock.

Dermatological

Severe skin reactions, sometimes fatal, including toxic epidermal necrolysis/Stevens-Johnson syndrome, bullous dermatitis and drug reaction with eosinophilia and systematic symptoms.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE**Symptoms**

A case of attempted suicide with amiodarone 2600 mg is reported in the literature. No clinical symptoms, change in heart rate or blood pressure were reported. The ECG revealed considerable lengthening of the QT interval and T wave inversion in the precordial leads with transient disappearance of R wave in leads V1 to V4, simulating an antero-septal infarction.

In another case of attempted suicide with amiodarone 8 g, the only symptom was profuse perspiration. No signs of cyanosis, dyspnoea or decreased sensitivity were found. No clinical side effects were documented over the monitored period of 3 months.

Overdosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances amiodarone should be temporarily withdrawn and if necessary β -adrenostimulants or glucagon given.

Treatment

In the event of ingestion of a toxic dose, gastric lavage should be employed to reduce absorption and in addition general supportive measures should be applied.

For information on the management of overdosage, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Amiodarone is a Class III antiarrhythmic agent prolonging the action potential duration and hence refractory period of atrial, nodal and ventricular tissues, thereby giving a very broad spectrum of activity. An increase in the refractory period of the atrial cells is a major contributing action to the control of atrial tachyarrhythmias.

A reduction in the permeability of the atrioventricular node, both anterograde and retrograde, explains the efficacy of the drug in nodal tachycardias caused by re-entry through the atrioventricular node.

Its action on ventricular arrhythmias is explained by a number of mechanisms. The effect on the atrium and atrioventricular node results in a reduction in the frequency of stimuli reaching the ventricle thus giving the ventricular cell mass time to repolarise in cases where there has been desynchronisation of the refractory periods. Furthermore, a lengthening of the refractory period of the His-Purkinje system and ventricular contractile fibres reduces or prevents micro re-entry. Amiodarone increases coronary blood flow, decreases cardiac oxygen requirements without producing negative inotropic effects and also suppresses ectopic pacemakers, and this is particularly valuable in arrhythmias associated with ischaemic damage or angina pectoris.

The site and mode of action of amiodarone can be summarised in terms of its effect on myocardial electrophysiology:

Myocardial Electrophysiology

Sinus Node. It decreases sinus automaticity by reducing the slow diastolic depolarisation gradient in the nodal cell. This is a direct effect and is not mediated through the sympathetic or parasympathetic system.

Atrioventricular (A-V) Node. It reduces the speed of conduction and increases the refractory period of the atrioventricular node.

His-Purkinje System. It increases the refractory period but does not modify the speed of conduction of the His-Purkinje system.

Contractile Fibres. It increases the action potential but does not alter the rate of depolarisation of the atrial or ventricular myocardial cells; an effect that is more marked in the atria than the ventricles.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

In general, pharmacokinetic data relating to amiodarone are incomplete.

Absorption

Amiodarone is incompletely and erratically absorbed following oral administration. Absolute bioavailability ranges from 22 to 86% but there is extensive inter-subject variation.

Distribution

An HPLC method is available for estimation of amiodarone plasma levels. However, the value of this is limited because the correlation of therapeutic effect and plasma level has not been established. Steady state plasma levels are generally around 1 to 2 µg/mL, although inter-subject variations are common.

Considerably higher values have been reported, especially subsequent to large single doses. Peak plasma concentrations of 6.9 ± 4.2 µg/mL have been recorded following a single dose of 1600 mg and 1.7 ± 0.3 µg/mL after a single dose of 800 mg. Steady state levels of 1.57 ± 0.1 µg/mL and 3.9 µg/mL have been recorded after daily oral dosing in the range 800 to 1800 mg.

The half-life of amiodarone is long and with chronic oral dosing can be from 14 to 110 days but is usually in the range 14 to 59 days. The principal metabolite of amiodarone, which has been detected in the plasma and other tissues, is desethylamiodarone. This metabolite is reported to have a longer half-life than amiodarone ie. 10 hours after a single dose of amiodarone and 60 to 90 days after chronic dosing with amiodarone. The activity of this metabolite is not known. Amiodarone is highly protein bound and is thought to bind strongly to protein at concentrations of 10 µg/mL.

The apparent volume of distribution after oral (200 to 400 mg) amiodarone is 6.31 ± 4.93 L/kg. Amiodarone appears to accumulate in adipose tissue and in highly perfused organs (lung, bone marrow, adrenals, liver, pancreas, heart, spleen and kidney). The concentration of amiodarone in packed red blood cells is approximately 60% of that in plasma.

Metabolism

First pass metabolism in the gut wall and/or in the liver may be a factor in determining the availability of the drug.

Excretion

It is believed that most of the drug is excreted via the liver and gastrointestinal tract by biliary excretion. There may be some hepatic recirculation.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

In a carcinogenicity study in rats, amiodarone caused a dose related increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes. Although mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is proposed for this type of tumour induction. In the mouse, carcinomas were not observed but dose dependent thyroid follicular hyperplasia was seen. The relevance of these findings to man is unknown. Clinical experience has indicated that amiodarone can affect thyroid function.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- lactose monohydrate
- microcrystalline cellulose
- povidone

- crosprovidone
- colloidal anhydrous silica
- purified talc
- magnesium stearate

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/Al blister packs

Pack sizes: 30's

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 32514 – ARATAC 200 AMIODARONE HYDROCHLORIDE 200 mg tablet blister pack

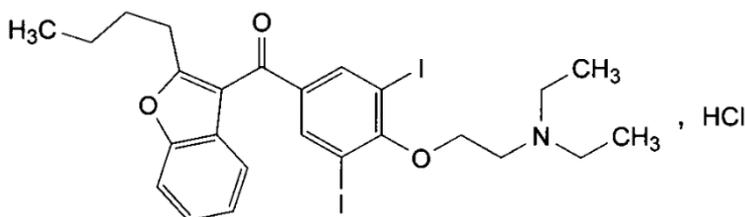
AUST R 32519 – ARATAC 100 AMIODARONE HYDROCHLORIDE 100 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical name: (2-n-butyl-3-[4-(2-diethylaminoethoxy)-3,5-diiodobenzoyl]benzofuran hydrochloride)

Molecular formula: C₂₅H₂₉I₂NO₃.HCl

Molecular weight: 681.8

Amiodarone hydrochloride is a fine white crystalline powder. It is slightly soluble in water and is soluble in alcohol and chloroform. It is an amphiphilic compound and contains iodine in its formulation. Each 200 mg tablet of amiodarone contains approximately 75 mg organic iodine and, in the steady state, metabolism of 300 mg amiodarone yields 9 mg/day of iodine.

CAS Number

199774-82-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

30/10/1991

10 DATE OF REVISION

21/01/2022

Summary Table of Changes

Section Changed	Summary of New Information
2	Update to declare S1 ingredient to align with current artwork.
8	Update to sponsor details.
2, 6.5	Editorial Changes

ARATAC is a Viatrix company trade mark.

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