NEW ZEALAND DATA SHEET

ARATAC

1. Product Name

Aratac, 100 mg and 200 mg tablet.

2. Qualitative and Quantitative Composition

Each Aratac tablet contains 100 mg or 200 mg of amiodarone (as hydrochloride).

Aratac tablets contain lactose. For the full list of excipients, see section 6.1.

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. In the steady state, metabolism of 300 mg amiodarone yields 9 mg/day of iodine.

3. Pharmaceutical Form

Amiodarone 100 mg Tablet: round, normal convex, white tablet, 8.5 mm diameter, imprinted “AM” | “100” on one side and “G” on the other.

Amiodarone 200 mg Tablet: round, normal convex, white tablet, 10.0 mm diameter, imprinted “AM” | “200” on one side and “G” on the other.

The tablet can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

Treatment should be initiated only under hospital or specialist supervision.

Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome. Atrial flutter and fibrillation when other agents cannot be used.

All types of tachyarrhythmias of paroxysmal nature including: supraventricular, nodal and ventricular tachycardias, ventricular fibrillation; when other agents cannot be used. Tablets are used for stabilisation and long term treatment.

4.2 Dose and method of administration

Dose

Due to poor absorption and wide inter-patient variability of absorption, the initial loading and subsequent maintenance dosage schedules of the medicine 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 generally effective.

Initial stabilisation

Treatment should be started with 200 mg, 3 times a day and may be continued for one 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.

General considerations

The high initial dose is necessary because of the slow onset of action whilst the necessary tissue levels of amiodarone are achieved. Amiodarone has a low acute toxicity and in this initial treatment period serious problems have not been reported. However, excessive dosage during maintenance therapy can cause side effects which are believed to be related to excessive tissue retention of amiodarone and/or its metabolites. Side effects slowly disappear as the tissue levels fall after the dosage is reduced or the agent withdrawn. If the agent is withdrawn, residual tissue bound amiodarone may protect the patient for up to a month, 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 clinical features of excessive dosage are detected and the dosage adjusted accordingly. It is particularly important that the minimum effective dose be used.

Special populations

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 (see section 4.4).

4.3 Contraindications

Known hypersensitivity to iodine or amiodarone or to any of the excipients listed in section 6.1.

Pregnancy and lactation (see section 4.6).

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, amiodarone should only be used in conjunction with a pacemaker.

Sinus bradycardia and sino-atrial heart block.

Amiodarone is contraindicated in patients with evidence, or a history of thyroid dysfunction.

Combined therapy with medicines which may induce Torsades de Pointes (see section 4.5).

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), 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

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 L-Thyroxine. The dose of L-Thyroxine 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 therapeutic 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. However these changes do not reflect toxicity.

Amiodarone 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 cardiotonic 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). 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 onset of 2nd or 3rd degree A-V 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).

Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone is used in combination with sofobuvir 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 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 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 medicine. Prolongation of the actual QT above 0.60 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; Torsades 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) 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). 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) 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.

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) 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 disease

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

Skin reaction

Photosensitivity is quite common (see section 4.8) 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) regime (see section 4.8).

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 medicine, the neurological complication is slowly and incompletely resolved.

Use in renal disease

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

Paediatric use

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

Use in the elderly

In the elderly, heart rate may decrease markedly.

4.5 Interaction with other medicines and other forms of interaction

Medicine 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 .

Pharmacodynamic interactions

Drugs inducing Torsades de Pointes

Combined therapy with medicines that may induce Torsades de Pointes is contraindicated (see section 4.3):

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 increased significantly with co-administration 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) 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 medicines is not recommended:

Beta Adrenergic Blocking Medicines: amiodarone itself exhibits non-competitive alpha and beta 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 medicines of the calcium antagonist type (e.g. verapamil, diltiazem), may lead to undue bradycardia and conduction disorders may occur.

MAO Inhibitors: co-administration with monoamine oxidase (MAO) inhibitors is contraindicated on theoretical grounds.

Agents which may induce hypokalaemia

Combined therapy with the following agents is not recommended:

Stimulant 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 medicines in combination with amiodarone:

Diuretics inducing hypokalaemia: either alone or combined.

Systemic corticosteroids (gluco-, mineralo-); tetracosactrin.

Amphotericin B (IV).

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

General anaesthesia

Potentially severe complications have been reported in patients undergoing general anaesthesia, such as bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output (see sections 4.4 and 4.8).

A few cases of severe respiratory complications, such as adult acute respiratory distress syndrome, resulting 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 other 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-glycoprotein substrates

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

Digitalis (Digoxin): 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.

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.

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.

CYP 2D6 substrates

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

CYP 3A4 substrates

When such medicines are co-administered with amiodarone, an inhibitor of CYP 3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity:

Cyclosporin: 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: lignocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, colchicine.

Effect of other medicinal products on 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.

Co-administration 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 co-administration cannot be avoided, cardiac monitoring is recommended (see section 4.4).

Consideration should be given to the possibility that amiodarone may alter the plasma concentration of other medicines particularly those which are highly protein bound.

Effect 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 medicine 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 medicines such as dexamethasone.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C

Because of the long half-life of amiodarone and its major metabolite, and the potential to cause abnormal thyroid function, the 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. Where 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 medicine 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) 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 medicine requires that the medicine 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.

Breast-feeding

As amiodarone and its desethyl metabolite are secreted in breast milk in significant quantities 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.

Fertility

No data available.

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 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 underlying disease state, and individual variation in pharmacokinetic profile of the medicine.

More common reactions

Biochemical abnormalities

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

Abnormal thyroid function tests (see section 4.5 – Effects on Laboratory Tests).

Cardiovascular

Atypical ventricular tachycardia (Torsades de Pointes)

Amiodarone-induced atypical ventricular tachycardia has been described. Earlier reports describe combination therapy in which other medicines, 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 medicine 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 (T4, T3 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 usTSH level should be measured when thyroid dysfunction is suspected.

The signs of thyroid hyperactivity to be sought are weight loss, asthenia, restlessness, recurrence of cardiac dysrhythmia, onset of angina or congestive heart failure. The diagnosis may be confirmed by the finding of an elevated serum triiodothyronine (T3), a low level of thyroid stimulating hormone (TSH) and a reduced TSH response to thyrotropin releasing hormone (TRH). (Elevation of reverse tri iodothyronine (rT3) 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 medicine is discontinued.

The clinical features of hypothyroidism such as weight gain, reduced activity and/or, excessive bradycardia with regard to the expected effect of amiodarone, should alert the clinician. 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 (T4), T3 and free thyroxine index (FTI) may be low.

Courses of anti-thyroid medicines have been used for the treatment of thyroid hyperactivity; large doses may be required initially.

Thyroid hypofunction may be treated cautiously with L-thyroxine.

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 results in most cases 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 neurolipidosis 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 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 medicine is withdrawn. Complete clearing is reported to occur from between 3 and 7 months after withdrawal of the medicine.

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 organizing 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 of suspected adverse reactions - Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

A case of attempted suicide with 2600 mg amiodarone is reported in the literature. No clinical symptoms, changes 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 8 g amiodarone, the only symptoms reported were 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 beta adrenostimulants or glucagon given. 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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cardiovascular therapy, antiarrhythmics, class III; ATC code: C01BD01

Amiodarone hydrochloride is a Class III antiarrhythmic agent. The active ingredient of Aratac is amiodarone hydrochloride (2-n-butyl-3(4-(2-diethylaminoethoxy)-3,5-diiodobenzoyl) benzofuran hydrochloride).

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 A-V node, both anterograde and retrograde, explains the efficacy of the medicine in nodal tachycardias caused by re-entry through the A-V node.

Its action on ventricular arrhythmias is explained by a number of mechanisms. The effect on the atrium and A-V 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.

Pharmacodynamic effects

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.

Atrio-ventricular (A-V) node

It reduces the speed of conduction and increases the refractory period of the A-V 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.

5.2 Pharmacokinetic properties

Absorption

In general, pharmacokinetic data relating to amiodarone are incomplete. Amiodarone is incompletely and erratically absorbed following oral administration. Absolute bioavailability ranges from 22 to 86% but there is extensive inter-subject variation. First-pass metabolism in the gut wall and/or in the liver may be a factor in determining the availability of the medicine.

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 800-1800 mg.

The apparent volume of distribution after oral (200-400 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.

Biotransformation

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 i.e. 10 hours after a single dose of amiodarone and 60-90 days after chronic dosing with amiodarone. The activity of this metabolite is not known.

Elimination

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. Amiodarone is highly protein bound and is thought to bind strongly to protein at concentrations of 10 µg/mL. It is believed that most of the medicine is excreted via the liver and gastrointestinal tract by biliary excretion. There may be some hepatic recirculation.

5.3 Preclinical safety data

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

Aratac tablets also contains:

- Lactose monohydrate
- Talc purified
- Cellulose microcrystalline
- Crospovidone
- Povidone
- Magnesium stearate
- Colloidal silicon dioxide

Aratac tablets are gluten free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Al/PVC/PVDC blister strips enclosed in a cardboard carton. Pack size of 30 tablets.

HDPE bottle with PP cap. Pack size of 30 tablets.

Not all pack types may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11-183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

19 December 1991

10. Date of Revision of the Text

08 May 2019

Section	
4.4	Addition of Primary graft dysfunction post cardiac transplant. Minor editorial changes.
4.5	Minor editorial changes.
4.8	Addition of Primary graft dysfunction post cardiac transplant
6.1	Re-organized excipient list