Professional Information for BIO-AMIODARONE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BIO-AMIODARONE 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg amiodarone hydrochloride.

Excipient with known effect:

Contains sugar (lactose monohydrate): 50 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Scored, flat, white tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of tachydysrhythmias associated with Wolff-Parkinson-White syndrome and other types of tachydysrhythmias of paroxysmal nature including supraventricular, nodal and ventricular tachycardia, atrial flutter, atrial fibrillation, and ventricular fibrillation when other medicines cannot be used.

4.2 Posology and method of administration

Posology

It is particularly important that the minimum effective dose be used. In all cases the patient management must be judged on the individual response and wellbeing.

Initial treatment:

The usual dosage is 200 mg, 3 times a day and may be continued for 1 week. The dosage should then be reduced to 200 mg twice daily for a further week.

Maintenance treatment:

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 dosage should be titrated to the minimum dosage required to maintain control of the dysrhythmia. The maintenance dose should be regularly reviewed, especially where this exceeds 200 mg daily.

Changeover from intravenous to oral therapy:

Oral therapy should be initiated concomitantly at the usual loading dose i.e., 200 mg three times a day, as soon as possible after an adequate response has been obtained using amiodarone intravenous, which should then be phased out gradually.

General considerations:

The high initial dose is necessary because of the slow onset of action whilst the necessary tissue levels of amiodarone are achieved. BIO-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after the dosage is reduced or BIO-AMIODARONE treatment withdrawn.

If BIO-AMIODARONE treatment is withdrawn, residual tissue-bound amiodarone may protect the patient for up to one month, but the likelihood of recurrence of cardiac dysrhythmias during this period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, and that the patient is monitored regularly to detect the clinical features of excess amiodarone dosage. Therapy may then be adjusted accordingly.

Use in elderly:

As with all patients it is important that the minimum effective dose is used. Elderly patients may be more susceptible to bradycardia and conduction defects if a too high a dose is employed. Particular attention should be paid to monitoring of thyroid function.

Method of administration

BIO-AMIODARONE is for oral administration.

4.3 Contraindications

- Sinus bradycardia and sino-atrial heart block. In patients with severe conduction disturbances (high grade AV block, bifascicular block) or sinus node disease, BIO-AMIODARONE should only be used in conjunction with a pacemaker.
- Hyperthyroidism; evidence or history of thyroid dysfunction. Thyroid function tests should be performed prior to and during therapy with BIO-AMIODARONE
- Known hypersensitivity to iodine.
- Medicines producing torsades de pointes (see section 4.5).

- Severe hypotension.
- Class Ia anti-dysrhythmic medicines namely sotalol.
- Pregnant or breastfeeding women.
- Avoid in patients with acute porphyria.
- BIO-AMIODARONE should not be administered to patients known to be allergic to amiodarone or any of the excipients (listed in section 6.1).
- Concomitant use of BIO-AMIODARONE and grapefruit juice should be avoided as the maximum plasma concentration of BIO-AMIODARONE is increased.
- Medicines such as astemizole, bepridil, IV erythromycin, halofantrin, pentamidin, sparfloxacin, sultopride, terfenadine, vincamin in combination with BIO-AMIODARONE increase the risk of potentially lethal torsades de pointes.
- Safety and efficacy of BIO-AMIODARONE in paediatric patients have not been established.

4.4 Special warnings and precautions for use

Due to substantial toxicity, BIO-AMIODARONE is intended for use only in patients with indicated life-threatening dysrhythmia. BIO-AMIODARONE has several potentially fatal toxicities of which the most important are pulmonary toxicity (hypertensive pneumonitis of interstitial/alveolar pneumonitis). Pulmonary toxicity has been fatal about 10 % of the time. Liver injury is common with BIO-AMIODARONE, but is usually mild and evidenced only by abnormal liver enzymes. Evident liver disease can occur, but has been fatal in a few cases. Like other anti-dysrhythmia medicine, BIO-AMIODARONE can exacerbate the dysrhythmia, e.g., by making the dysrhythmia less well tolerated or more difficult to reverse. This and significant heart block or sinus bradycardia should be manageable in the proper clinical setting in most cases. Although the frequency of such prodysrhythmic events does not appear greater with BIO-AMIODARONE than with many other medicines available, the effects are prolonged when they occur. Even in patients at high risk of dysrhythmic death, in whom the toxicity of BIO-AMIODARONE is an acceptable risk, BIO-

AMIODARONE poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilise alternative medicines first. The difficulty of using BIO-AMIODARONE effectively and safely itself poses a significant risk to patients. Patients with the indicated dysrhythmia must be hospitalised while the loading dose of BIO-AMIODARONE is given, a response generally require at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. On discontinuation of treatment, substituting BIO-AMIODARONE with other medicines is made difficult by the unpredictable, changing amiodarone body burden.

A similar problem exists when BIO-AMIODARONE is not effective: it poses the risk of interaction with whatever subsequent treatment is tried.

BIO-AMIODARONE can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system (see section 4.8). Because these reactions may be delayed, patients on long-term treatment should be carefully supervised. As undesirable effects are usually dose-related, the minimum effective maintenance dose should be given.

Before surgery, the anaesthetist should be informed that the patient is taking amiodarone (see section 4.5).

Cardiac disorders:

Too high a dosage 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 treatment should be withdrawn. If necessary, beta-adrenostimulants or glucagon may be given. Because of the long half-life of amiodarone, if bradycardia is severe and symptomatic the insertion of a pacemaker should be considered.

Oral amiodarone is not contraindicated in patients with latent or manifest heart failure, but caution should be exercised as, occasionally, existing heart failure may be worsened. In such cases, BIO-AMIODARONE may be used with other appropriate therapies.

The pharmacological action of amiodarone induces electrocardiogram (ECG) changes: QT prolongation (related to prolonged repolarisation) with the possible development of U-waves and deformed T-waves. These changes do not reflect toxicity.

In the elderly, heart rate may decrease markedly.

Treatment should be discontinued in case of onset of 2nd or 3rd degree A-V block, sino-atrial block or bifascicular block.

Amiodarone has a low pro-arrhythmic effect. Onsets of new dysrhythmias or worsening of treated dysrhythmias, sometimes fatal, have been reported. It is important, but difficult, to differentiate a lack of efficacy of the medicine from a proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Prodysrhythmic effects generally occur in the context of QT prolonging factors such as medicine interactions and/or electrolytic disorders (see sections 4.5. and 4.8). Despite QT interval prolongation, amiodarone exhibits a low torsadogenic activity.

Before starting BIO-AMIODARONE, it is recommended to perform an ECG and serum potassium measurement. Monitoring of ECG is recommended during treatment.

BIO-AMIODARONE may increase the defibrillation threshold and/or pacing threshold in patients with an implantable cardioverter defibrillator or a pacemaker, which may adversely affect the efficacy of

the device. Regular tests are recommended to ensure the proper function of the device after initiation of treatment or change in posology.

Severe bradycardia and heart block (see section 4.5):

Life-threatening cases of bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone.

Bradycardia has generally occurred within hours to days, but later cases have been mostly observed up to 2 weeks after initiating HCV treatment.

BIO-AMIODARONE should only be used in patients on sofosbuvir- containing regimen when other alternative anti-dysrhythmic treatments are not tolerated or are contraindicated.

Should concomitant use of amiodarone be considered necessary, it is recommended that patients undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Due to the long half-life of amiodarone, cardiac monitoring as outlined above should also be carried out for patients who have discontinued BIO-AMIODARONE within the past few months and are to be initiated on sofosbuvir-containing regimen.

All patients receiving amiodarone in combination with sofosbuvir-containing regimen should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should 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.

PGD is a life-threatening complication of heart transplantation that presents as left, right or biventricular dysfunction occurring within the first 24 hours of transplant surgery for which there is no identifiable secondary cause (see section 4.8). Severe PGD may be irreversible.

For patients who are on the heart transplant waiting list, consideration should be given to use an alternative anti-dysrhythmic medicine as early as possible before transplant.

Endocrine disorders (see section 4.8):

Thyroid function should be monitored regularly in order to detect BIO-AMIODARONE induced hyper- or hypothyroidism. Thyroxine, tri-iodothyronine and thyrotropin (thyroid stimulating hormone, TSH) concentration should be measured; clinical assessment alone is unreliable.

Monitoring should be carried out during treatment, at six-monthly intervals, and for several months following its discontinuation. This is particularly important in the elderly. In patients whose history indicates an increased risk of thyroid dysfunction, regular assessment is recommended. Serum usTSH level should be measured when thyroid dysfunction is suspected.

Hypothyroidism:

Hypothyroidism should be suspected if the following clinical signs occur: weight gain, cold intolerance, reduced activity, excessive bradycardia. The diagnosis is supported by an increase in serum usTSH and an exaggerated TSH response to TRH. T_3 and T_4 levels may be low. Euthyroidism is usually obtained within 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, such as weight loss, asthenia, restlessness, increase in heart rate, onset of arrhythmia, angina, congestive heart failure should alert the medical practitioner. The diagnosis is supported by a decrease in serum usTSH level, an elevated T_3 and a reduced TSH response to thyrotropin releasing hormone. Elevation of reverse T_3 (rT_3) may also be found.

In the case of hyperthyroidism, therapy should be withdrawn. Clinical recovery usually occurs within a few months, although severe cases, sometimes resulting in fatalities, have been reported. Clinical recovery precedes the normalisation of thyroid function tests.

Courses of anti-thyroid medicines have been used for the treatment of severe thyroid hyperactivity; large doses may be required initially. These may not always be effective and concomitant high dose corticosteroid therapy (e.g., 1 mg/kg prednisolone) may be required for several weeks.

Eye disorders (*see section 4.8*):

If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed. Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness. Unless blurred or decreased vision occurs, ophthalmological examination is recommended annually.

Hepato-biliary disorders (see section 4.8):

Amiodarone may be associated with a variety of hepatic effects, including cirrhosis, hepatitis, jaundice and hepatic failure. Some fatalities have been reported, mainly following long-term therapy, although rarely they have occurred soon after starting treatment. It is advisable to monitor liver function particularly transaminases before treatment and six monthly thereafter. The dose of BIO-

AMIODARONE should be reduced, or the treatment discontinued if the transaminases increase exceeds three times the normal range.

At the beginning of therapy, elevation of serum transaminases which can be in isolation (1,5 to 3 times normal) may occur. These may return to normal with dose reduction, or sometimes spontaneously.

Isolated cases of acute liver disorders with elevated serum transaminases and/or jaundice may occur; in such cases treatment should be discontinued.

There have been reports of chronic liver disease. Alteration of laboratory tests which may be minimal (transaminases elevated 1,5 to 5 times normal) or clinical signs (possible hepatomegaly) during treatment for longer than 6 months should suggest this diagnosis. Routine monitoring of liver function tests is therefore advised. Abnormal clinical and laboratory test results usually regress upon cessation of treatment, but fatal cases have been reported. Histological findings may resemble pseudo-alcoholic hepatitis, but they can be variable and include cirrhosis.

Although there have been no literature reports on the potentiation of hepatic adverse effects of alcohol, patients should be advised to moderate their alcohol intake while taking BIO-AMIODARONE.

Nervous system disorders (see section 4.8):
BIO-AMIODARONE may induce peripheral sensorimotor neuropathy and/or myopathy. Both these conditions may be severe, although recovery usually occurs within several months after amiodarone withdrawal but may sometimes be incomplete.

Respiratory, thoracic and mediastinal disorders (see section 4.8):

Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity (hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonitis. Presenting features can include dyspnoea (which may be severe and unexplained by the current cardiac status), non-productive cough and deterioration in general health (fatigue, weight loss and fever). The onset is usually slow but may be rapidly progressive.
Whilst the majority of cases have been reported with long term therapy, a few have occurred soon after starting treatment.

Patients should be carefully evaluated clinically, and consideration given to chest X-rays before starting therapy. During treatment, if pulmonary toxicity is suspected, this should be repeated and associated with lung function testing including, where possible, measurement of transfer factor. Initial radiological changes may be difficult to distinguish from pulmonary venous congestion. Pulmonary toxicity has usually been reversible following early withdrawal of amiodarone therapy, with or without corticosteroid therapy. Clinical symptoms often resolve within a few weeks followed by slower radiological and lung function improvement. Some patients can deteriorate despite discontinuing BIO-AMIODARONE.

Skin and subcutaneous tissue disorders (see section 4.8):
Patients should be instructed to avoid exposure to sun and to use protective measures during therapy as patients taking BIO-AMIODARONE can become unduly sensitive to sunlight, which may persist after several months of discontinuation of BIO-AMIODARONE. In most cases symptoms are limited to tingling, burning and erythema of sun-exposed skin but severe phototoxic reactions with blistering may be seen.

Severe bullous reactions:
Life-threatening or even fatal cutaneous reactions Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (see section 4.8). If symptoms or signs of SJS, TEN (e.g., progressive

skin rash often with blisters or mucosal lesions) are present amiodarone treatment should be discontinued immediately.

Caution is advised in patients with moderate or severe renal impairment because of the possibility of iodine accumulation.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take BIO-AMIODARONE.

4.5 Interaction with other medicines and other forms of interaction

Contraindicated combinations:

- Medicines such as astemizole, bepridil, IV erythromycin, halofantrin, pentamidin, sparfloxacin, sultopride, terfenadine, vincamin in combination with BIO-AMIODARONE increase the risk of potentially lethal torsades de pointes.
- Class Ia anti-dysrhythmic medicines (quinidine-like medicines, disopyramide) and sotalol increase the risk of potentially lethal torsades de pointes.

Inadvisable combinations:

- Stimulant laxatives also increase the risk of torsades de pointes. Use another type of laxative.
- Injectable diltiazem increases the risk of bradycardia and atrioventricular block. If this combination is deemed absolutely necessary, it should be used only under clinical supervision and continuous ECG monitoring.

Combinations requiring precautions of use:

- Beta-blockers and some calcium antagonists (verapamil, diltiazem): potentiation of bradycardia, sinus arrest and atrioventricular (AV) block results.
- Hypokalaemic medicines (risk of torsades de pointes).

- Hypokalaemic diuretics used alone or in combination.
- Steroids (systemically used gluco- and mineralocorticosteroids), tetracosactide and IV administered amphotericin B.
- Hypokalaemia should be prevented (and where necessary corrected). QT interval should be monitored, and in case of torsades de pointes, anti-dysrhythmic medicines should not be administered (electrosystolic stimulation and IV magnesium sulphate).
- BIO-AMIODARONE may potentiate oral anticoagulant therapy by increasing levels of the oral anticoagulant, e.g., warfarin. Prothrombin time/INR should be monitored more frequently during and after treatment with BIO-AMIODARONE.
- Co-administration of digoxin and BIO-AMIODARONE can increase the plasma concentration of digoxin and lead to excessive bradycardia and atrioventricular conduction disturbances. Clinical supervision, ECG monitoring and dosage adjustments may be required.
- Phenytoin: increase in phenytoin plasma concentrations with signs of overdosage (particularly neurological signs) can occur when used concurrently with BIO-AMIODARONE. Clinical supervision and a reduction in phenytoin dose are required as soon as overdosage signs occur.

General anaesthetics:

Potentially serious complications have been reported when BIO-AMIODARONE is combined with general anaesthetics. These complications include: atropine resistant bradycardia, hypotension, conduction disturbances and a decrease in cardiac output.

Some cases of acute respiratory distress have been observed just after cardiovascular surgery.

Possible potentiation of oxygen toxic effect has been suggested and the anaesthetist should be informed that the patient is taking BIO-AMIODARONE.

Medicines metabolised by cytochrome P450 3A4:

When such medicines are co-administered with ARYCOR, an inhibitor of CYP3A4, it may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity:

- *Ciclosporin:* plasma levels of ciclosporin may increase as much as 2-fold when used in combination. A reduction in the dose of ciclosporin may be necessary to maintain the plasma concentration within the therapeutic range.
- *Statins:* the risk of muscular toxicity (e.g., rhabdomyolysis) 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 BIO-AMIODARONE.
- *Other medicines metabolised by cytochrome P450 3A4:* examples of such medicines are lidocaine (lignocaine), sirolimus, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine, ergotamine and colchicine.

CYP 2D6 substrates:

*G*iven that flecainide is mainly metabolised by CYP 2D6, by inhibiting this isoenzyme, amiodarone may increase flecainide plasma levels. It is advised to reduce the flecainide dose by 50 % and to monitor the patient closely for adverse effects. Monitoring of flecainide plasma levels is strongly recommended in such circumstances.

Dabigatran:

Caution should be exercised when BIO-AMIODARONE is co-administered with dabigatran due to the risk of bleeding. It may be necessary to adjust the dosage of dabigatran.

Effects of other products on amiodarone:

- CYP3A4 inhibitors and CYP2C8 inhibitors may have a potential to inhibit amiodarone metabolism and to increase its exposure. It is recommended to avoid CYP 3A4 inhibitors during treatment with BIO-AMIODARONE.
- Concomitant use of BIO-AMIODARONE and grapefruit juice should be avoided as the maximum plasma concentration of BIO-AMIODARONE is increased.

- Co-administration of amiodarone with sofosbuvir containing regimens may lead to serious symptomatic bradycardia. If co-administration cannot be avoided, cardiac monitoring is recommended.

4.6 Fertility, pregnancy and lactation

BIO-AMIODARONE is contraindicated in pregnancy and during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

The ability to drive or to operate machinery may be impaired in patients with clinical symptoms of amiodarone-induced eye disorders.

4.8 Undesirable effects

Side effects may not appear until several days, weeks or years after initiation of BIO-AMIODARONE therapy and may persist for several months after withdrawal.

Blood and lymphatic system disorders

Less frequent: Haemolytic anaemia, aplastic anaemia, thrombocytopenia.

Frequency unknown: Neutropenia, agranulocytosis.

In patients taking amiodarone there have been incidental findings of bone marrow granulomas. The clinical significance of this is unknown.

Immune system disorders

Frequency unknown: Some isolated cases varying in aspect have been observed suggesting hypersensitivity reactions that include vasculitis, renal impairment with moderate increase in creatinine, and thrombocytopenia, angioneurotic oedema (Quincke's oedema), anaphylactic shock/anaphylactoid reaction including chock.

Endocrine disorders

Frequent: Hyperthyroidism (sometimes fatal), hypothyroidism.

Less frequent: Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

In case of hyperthyroidism, BIO-AMIODARONE should be withdrawn.

Metabolism and nutrition disorders:

Frequency unknown: Decreased appetite.

Psychiatric disorders

Frequent: Libido decreased.

Frequency unknown: Confusional state, delirium, hallucination.

Nervous system disorders

Frequent: Neurotoxicity, nightmares, sleeplessness, extrapyramidal tremor (for which regression usually occurs after reduction of dose or withdrawal).

Less frequent: Sensory-motor peripheral neuropathy and/or myopathy (usually reversible with treatment discontinuation), headache, cerebellar-like ataxia (for which regression usually occurs after reduction of dose or withdrawal), benign intracranial hypertension, vertigo.

Frequency unknown: Parkinsonism, parosmia.

Eye disorders

Frequent: Cortical micro-deposits develop in the majority of patients, usually limited to the area under the pupil, which are usually only discernible by slit-lamp examinations. They may be associated with coloured halos. These are

reversible on stopping therapy. The deposits are considered essentially benign and do not require discontinuation of BIO-AMIODARONE.

Less frequent: Ocular toxicity including optic neuropathy and/or optic neuritis that may progress to blindness.

During long-term therapy regular ophthalmologic examination is recommended.

Cardiac disorders

Frequent: Bradycardia (generally moderate and dose-related).

Less frequent: Dysrhythmias, new or exacerbated (sometimes followed by cardiac arrest), congestive heart failure, sinus bradycardia, conduction disturbances (sino-atrial block, atrioventricular blocks of various degrees).

Frequency unknown: Torsades de pointes (see sections 4.4 and 4.5).

Vascular disorders

Frequent: Hypotension.

Less frequent: Vasculitis.

Respiratory, thoracic and mediastinal disorders

Frequent: Pulmonary fibrosis or interstitial pneumonitis/alveolitis, pleuritis, bronchiolitis obliterans organising pneumonia (BOOP).

Test of pulmonary function should be carried out regularly in patients on long-term therapy. These pulmonary effects may be potentially fatal although reversible on withdrawal.

Less frequent: Bronchospasm (in patients with severe respiratory failure and especially in asthmatic patients), surgery (possible interaction with a high oxygen concentration).

There have been some reports of pulmonary haemorrhage, although exact frequencies are not known.

Gastrointestinal disorders

Frequent: Benign gastrointestinal disorders (nausea, vomiting, dysgeusia), metallic taste, constipation.

These are usually occurring with loading dosage and resolving with dose reduction.

Less frequent: Dry mouth.

Frequency unknown: Pancreatitis.

Hepato-biliary disorders

Frequent: Isolated increases in transaminases (see section 4.4), acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure (which are sometimes fatal).

Less frequent: Chronic liver disease (pseudo alcoholic hepatitis, cirrhosis), sometimes fatal.

Skin and subcutaneous tissue disorders

Frequent: Photosensitivity (particularly to long wave UVA light), eczema. Blue-grey colouring of skin on face, neck and arms, in case of prolonged treatment with high daily dosages; such pigmentations slowly disappear following treatment discontinuation.

Less frequent: Cases of erythema have been reported during radiotherapy, skin rashes (usually non-specific), exfoliative dermatitis, alopecia.

Frequency unknown: Urticaria, severe skin reactions sometimes fatal including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), bullous dermatitis, drug reaction with eosinophilia and systematic symptoms (DRESS).

Musculoskeletal and connective tissue disorders:

Frequency unknown: Lupus like syndrome.

Reproductive system and breast disorders

Less frequent: Non-infectious epididymitis, impotence.

General disorders and administration site conditions

Frequency unknown: Granuloma, including bone marrow granuloma.

Investigations

Less frequent: Increase in blood creatinine.

Injury, poisoning and procedural complications

Frequency unknown: Primary graft dysfunction post cardiac transplant (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BIO-AMIODARONE is important. It allows continued monitoring of the benefit/risk balance of BIO-AMIODARONE. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdosage may lead to severe bradycardia, conduction disturbances or spontaneously reversible episodes of ventricular tachycardia. In these cases, BIO-AMIODARONE should be withdrawn. In addition to supportive measures, gastric lavage may be used to reduce absorption. If bradycardia continues, a beta-adrenostimulant or glucagon may be administered.

Most often, it remains asymptomatic. However, because of the product's kinetics, sufficient prolonged monitoring, especially cardiac monitoring, is recommended. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.6.2 Cardiac depressants.

Pharmacotherapeutic group: Antiarrhythmics, class III.

ATC code: C01B D01.

Amiodarone is an anti-dysrhythmic compound belonging to class III anti-dysrhythmic medicines.
Amiodarone prolongs the duration of the action potential, particularly in the nodal and Purkinje tissue. Amiodarone does not appear to alter the resting membrane potential, but depresses membrane responsiveness and prolongs the refractory period in the atria, AV node, His-Purkinje system, ventricles and accessory atrio-ventricular conduction pathways. The conduction rate is reduced in the atria, AV node and accessory pathways.
Amiodarone also demonstrates non-competitive alpha and beta adrenoreceptor antagonism.

5.2 Pharmacokinetic properties

Amiodarone is strongly protein bound (96 %) and the plasma half-life is usually approximately 50 days. However, there may be considerable inter-patient variation.
A major metabolite, desethylamiodarone, has anti-dysrhythmic properties. There is very little urinary excretion of amiodarone or its metabolites, the major route of excretion being in faeces via the bile; some enterohepatic recycling may occur. Amiodarone and desethylamiodarone are reported to cross the placenta and to be distributed into breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Lactose monohydrate

Povidone

Magnesium stearate

Colloidal anhydrous silica

Pregelatinised starch.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Do not remove the blisters from the cartons until required for use.

6.5 Nature and contents of container

Boxes containing 30 tablets in PVC/ALU blister.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark, Midrand 1685

South Africa

8. REGISTRATION NUMBER

34/6.2/0119

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2003

10. DATE OF REVISION OF THE TEXT

15 March 2023.