SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

MYORYTHM 100, Tablet

MYORYTHM 200, Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MYORYTHM 100, tablet contains 100 mg Amiodarone Hydrochloride

Each MYORYTHM 200, tablet contains 200 mg Amiodarone Hydrochloride

Contains sugar.

MYORYTHM 100 contains 58,25 mg lactose monohydrate per tablet.

MYORYTHM 200 contains 116,50 mg lactose monohydrate per tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

MYORYTHM 100: Light pink to pink, round, debossed with “A” on one side and “100” on other side.

MYORYTHM 200: Light pink to pink, debossed with “A vertical scoreline A (A|A)” on one side and “200” on other side.

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 tachycardias, atrial flutter and 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’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 three 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

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 100 mg tablet should be used to titrate 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 HCl intravenous injection, 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. Amiodarone as contained in MYORYTHM 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 treatment withdrawn.

If MYORYTHM 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.

Special populations

Use in the elderly

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 employed. Particular attention should be paid to monitoring of thyroid function (see section 4.3 and section 4.4).

Paediatric population

The safety and efficacy of amiodarone in children has not been established (see section 4.3).

Method of administration

Oral use.

4.3 Contraindications

MYORYTHM is contraindicated in:

- Hypersensitivity to the active substance, amiodarone, or to iodine or to any of the excipients (see section 6.1). (One tablet of MYORYTHM 100 contains 37,5 mg iodine and one tablet of MYORYTHM 200 contains 75 mg iodine);
- sinus bradycardia, sino-atrial heart block. In patients with sick sinus syndrome (risk of sinus arrest), severe atrioventricular conduction disorders (high grade AV block, bifascicular or trifascicular block) or sinus node disease, unless a pacemaker is fitted;
- thyroid dysfunction (see section 4.4). Thyroid function tests should be performed in all patients prior to therapy;
- pregnancy and lactation (see section 4.6);
- combined therapy with medicines which may induce Torsades de Pointes (see section 4.5); or
- Paediatric Patients: The safety and efficacy of MYORYTHM in paediatric patients have not been established. Therefore, its use in paediatric patients is not recommended.

4.4 Special warnings and precautions for use

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 MYORYTHM (see sections 4.5 and 4.8).

MYORYTHM should be avoided in patients with porphyria as it may precipitate an attack.

Cardiac disorders (see section 4.8):

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, MYORYTHM 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.

MYORYTHM 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, MYORYTHM may be used with other appropriate therapies.

The pharmacological action of amiodarone induces 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-dysrhythmic 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 pro-dysrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Pro-dysrhythmic 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 MYORYTHM treatment, it is recommended to perform an ECG and serum potassium measurement. Monitoring of ECG is recommended during treatment.

MYORYTHM 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 (e.g., MYORYTHM.)

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

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

All patients receiving MYORYTHM 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.

MYORYTHM is intended for use only in patients with the indicated life-threatening dysrhythmias because its use is accompanied by substantial toxicity. MYORYTHM has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease in some series of patients with ventricular dysrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of some patients. Pulmonary toxicity has been fatal.

Liver injury is common with MYORYTHM, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases.

MYORYTHM can exacerbate the dysrhythmias e.g., by making the dysrhythmias less well-tolerated or more difficult to reverse. This has occurred in patients in various series, and significant heart block or sinus bradycardia has been seen. Due to the long elimination half-life of MYORYTHM, the risk of pro-dysrhythmic effects is prolonged after amiodarone is stopped.

Even in patients at high risk of dysrhythmic death, in whom the toxicity of MYORYTHM is an acceptable risk, MYORYTHM 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 MYORYTHM effectively and safely itself poses a significant risk to patients.

Patients with the indicated dysrhythmias must be hospitalised while the loading dose of MYORYTHM is given, a response generally requires 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. In a retrospective survey of 192 patients with ventricular tachydysrhythmias, 84 required dosage reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported overall frequencies of discontinuation due to adverse reactions.

The time at which a previously controlled life-threatening dysrhythmia will recur after discontinuation or dosage adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalisation. Attempts to substitute other anti-dysrhythmic medicines when MYORYTHM must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when MYORYTHM is not effective: it still poses the risk of interaction with whatever subsequent treatment is tried.

Endocrine disorders (see section 4.8)

MYORYTHM may induce hypothyroidism or hyperthyroidism, particularly in patients with a personal history of thyroid disorders. Clinical and biological [including ultrasensitive Thyroid Stimulating Hormone (usTSH)]

monitoring should be performed prior to therapy in all patients. 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.

MYORYTHM contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T_3, free-T_4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of levothyroxine (T_4) to triiodothyronine (T_3) and may cause isolated biochemical changes (increase in serum free-T_4, free-T_3 being slightly decreased or even normal) in clinically euthyroid patients. There is no reason in such cases to discontinue amiodarone treatment if there is no clinical or further biological (usTSH) evidence of thyroid disease.

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 MYORYTHM treatment, or, up to several months after discontinuation. Clinical features, such as weight loss, asthenia, restlessness, increase in heart rate, onset of dysrhythmia, 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 medicine 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 MYORYTHM withdrawal due to the potential progression to blindness.

Unless blurred or decreased vision occurs, ophthalmologic examination is recommended annually during long-term treatment.

Hepato-biliary disorders (see section 4.8)

MYORYTHM 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 they have occurred soon after starting treatment particularly after amiodarone HCl intravenous injection. It is advisable to monitor liver function particularly transaminases before treatment and six monthly thereafter. MYORYTHM dose 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 MYORYTHM.

Nervous system disorders (see section 4.8)

MYORYTHM may induce peripheral sensorimotor neuropathy and/or myopathy. Both these conditions may be severe, although recovery usually occurs within several months after MYORYTHM 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 MYORYTHM.

Skin and subcutaneous tissue disorders (see section 4.8)

MYORYTHM may induce photosensitisation in some patients.

Patients should be instructed to avoid exposure to sun and to use protective measures, avoid exposure to sunlight and to use total sun block barrier creams and other protective measures, during therapy as patients taking MYORYTHM can become unduly sensitive to sunlight, which may persist after several months of discontinuation of MYORYTHM. 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.

Medicine interactions (see section 4.5)

Concomitant use of MYORYTHM is not recommended with the following medicine: beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem), stimulant laxative medicines which may cause hypokalaemia.

Increased plasma levels of flecainide have been reported with co-administration of MYORYTHM. The flecainide dose should be reduced accordingly and the patient closely monitored.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take MYORYTHM.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

- Medicine inducing Torsade de Pointes or prolonging QT

Medicine inducing Torsade de Pointes:

Combined therapy with the following medicine which prolong the QT interval is contraindicated (see section 4.3) due to the increased risk of Torsades de Pointes; for example:

- Class Ia anti-dysrhythmic medicine e.g., quinidine, disopyramide, procainamide;
- class III anti-dysrhythmic medicine e.g., sotalol, bretylium;
- intravenous erythromycin, co-trimoxazole or pentamidine injection;
- some anti-psychotics e.g., chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpiride and sertindole;
- lithium and tricyclic anti-depressants e.g., doxepin, maprotiline, amitriptyline;
- certain antihistamines e.g., terfenadine, astemizole, mizolastine;
- non-antidysrhythmic medicines such as vincamine, some neuroleptic medicines, cisapride;
- anti-malarial e.g., quinine, mefloquine, chloroquine, halofantrine; or
- moxifloxacin.

Medicines prolonging QT interval:

Co-administration of MYORYTHM with medicine known to prolong the QT interval (such as clarithromycin) must be based on a careful assessment of the potential risks and benefits for each patient since the risk of Torsade de Pointes may increase and patients should be monitored for QT prolongation.

Concomitant use of MYORYTHM with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contraindicated). There have been reports of QTc interval prolongation, with or without Torsades de Pointes, in patients taking MYORYTHM with fluoroquinolones (see section 4.3).

Medicine lowering heart rate or causing automaticity or conduction disorders

Combined therapy with the following medicine is not recommended:

Beta blockers and heart rate lowering calcium channel inhibitors (diltiazem, verapamil); potentiation of negative chronotropic properties and conduction slowing effects may occur.

Medicine which may induce hypokalaemia

Combined therapy with the following medicine is not recommended:

Stimulant laxatives, which may cause hypokalaemia thus increasing the risk of Torsades de Pointes; other types of laxatives should be used.

Caution should be exercised over combined therapy with the following medicine which may also cause hypokalaemia and/or hypomagnesaemia, e.g., diuretics, systemic corticosteroids (gluco-, mineralo-), intravenous amphotericin.

In cases of hypokalaemia, corrective action should be taken and QT interval monitored. In case of Torsades de Pointes anti-dysrhythmic medicines should not be given; pacing may be instituted, and IV magnesium may be used.

General anaesthesia

Caution is advised in patients undergoing general anaesthesia, or receiving high dose oxygen therapy.

Potentially severe complications have been reported in patients taking MYORYTHM undergoing general anaesthesia: bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output.

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

Effect of MYORYTHM on other medicines

MYORYTHM and/or its metabolite, desethylamiodarone, inhibit CYP1A1, CYP1A2, CYP3A4, CYP2C9, CYP2D6 and P-glycoprotein 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.

- PgP substrates
  MYORYTHM is a P-gp inhibitor. Co administration with P-gp substrates is expected to result in an increase of their exposure:
- Digitalis: administration of MYORYTHM to a patient already receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels. Clinical, ECG and biological monitoring is recommended and digoxin dosage should be halved. A synergistic effect on heart rate and atrioventricular conduction is also possible.
- Dabigatran: caution should be exercised when MYORYTHM 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
  MYORYTHM raises the plasma concentrations of oral anticoagulants (warfarin) and phenytoin by inhibition of CYP 2C9.
- Warfarin: the dose of warfarin should be reduced accordingly. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended.
- Phenytoin: phenytoin dosage should be reduced if signs of overdosage appear (resulting in neurological signs), and plasma levels may be measured.
- CYP P450 3A4 substrates
  When such medicine is co-administered with MYORYTHM, 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: 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 MYORYTHM 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 MYORYTHM.
- Other medicine metabolised by cytochrome P450 3A4: examples of such medicine are lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine, ergotamine and colchicine. Medicine metabolised by CYP 3A4 increases the risk of muscular toxicity.
- CYP 2D6 substrates

  Flecainide: given 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.

Effect of other substances on MYORYTHM

CYP3A4 inhibitors and CYP2C8 inhibitors may have a potential to inhibit MYORYTHM metabolism and to increase its exposure.

It is recommended to avoid CYP 3A4 inhibitors during treatment with MYORYTHM.

Grapefruit juice inhibits cytochrome P450 3A4 and may increase the plasma concentration of MYORYTHM. Grapefruit juice should be avoided during treatment with oral amiodarone.

Other medicine interactions with MYORYTHM (see section 4.4)

Coadministration of MYORYTHM with sofosbuvir-containing regimens may lead to serious symptomatic bradycardia.

If coadministration cannot be avoided, cardiac monitoring is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

In view of its effect on the foetal thyroid gland, MYORYTHM is contraindicated during pregnancy.

MYORYTHM should only be considered in pregnancy if no alternate therapy is available and dysrhythmias are life threatening. Under these circumstances the mother/parent(s) should be counselled regarding harmful effects of MYORYTHM on the foetus, and written consent given thereto (see section 4.3).

Breastfeeding

Amiodarone is excreted into the breast milk in significant quantities and breastfeeding is contraindicated (see section 4.3).

Fertility

There are no data on fertility.

4.8 Undesirable effects

System organ class	Frequency	Adverse Reaction
Blood and lymphatic system disorders	*Less frequent*	Haemolytic anaemia, aplastic anaemia, thrombocytopenia
	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*	Angioedema (Quincke's Oedema), anaphylactic shock/ anaphylactoid reaction including shock
Endocrine disorders (see section 4.4)	*Frequent*	Hypothyroidism, hyperthyroidism, sometimes fatal
	Less frequent	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	*Less frequent*	Decreased appetite
Psychiatric disorders	*Frequency unknown*	Confusional state/delirium
Nervous system disorders	*Frequent*	Extrapyramidal tremor, for which regression usually occurs after reduction of dose or withdrawal; nightmares, sleep disorders
	Less frequent	Peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the medicine; cerebellar ataxia, for which regression usually occurs after reduction of dose or withdrawal; benign intracranial hypertension (pseudo-tumor cerebri); headache; vertigo, ataxia, fatigue
	Frequency unknown	Parkinsonism, parosmia
Eye disorders	*Frequent*	Corneal microdeposits usually limited to the area under the pupil, which are usually only discernable by slit-lamp examinations. They may be associated with coloured halos in dazzling light or blurred vision. Corneal micro-deposits consist of complex lipid deposits and are reversible following discontinuation of treatment. The deposits are considered essentially benign and do not require discontinuation of amiodarone.
	Less frequent	Optic neuropathy/ neuritis that may progress to blindness (see section 4.4). Papilloedema, corneal degeneration, photosensitivity, eye discomfort, scotoma, lens opacities and macular degeneration have also been reported.
Cardiac disorders	*Frequent*	Bradycardia, generally moderate and dose-related ECG changes, i.e., QT interval lengthening corresponding to prolonged repolarisation; U-waves and deformed T-waves may occur.
	Less frequent	Onset or worsening of dysrhythmia, 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.
	Frequency unknown	Torsade de pointes
Vascular disorders	*Less frequent*	Vasculitis
Respiratory, thoracic and mediastinal disorders	*Frequent*	Pulmonary toxicity [hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis,

System organ class	Frequency	Adverse Reaction
		bronchiolitis obliterans organising pneumonia (BOOP)], sometimes fatal
	Less frequent	Bronchospasm in patients with severe respiratory failure and especially in asthmatic patients; surgery (possible interaction with a high oxygen concentration)
	Frequency unknown	Pulmonary haemorrhage (there have been some reports of pulmonary haemorrhage, although exact frequencies are not known)
Gastrointestinal disorders	*Frequent*	Benign gastrointestinal disorders (nausea, vomiting, dysgeusia) usually occurring with loading dosage and resolving with dose reduction; constipation
	Less frequent	Dry mouth
	Frequency unknown	Pancreatitis/acute pancreatitis
Hepato-biliary disorders (see section 4.4)	*Frequent*	Isolated increase in serum transaminases, which is usually moderate (1.5 to 3 times normal range), occurring at the beginning of therapy. It may return to normal with dose reduction or even spontaneously; 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; slate grey or bluish pigmentations of light-exposed skin, particularly the face, in case of prolonged treatment with high daily dosages; such pigmentations slowly disappear following treatment discontinuation; eczema
	Less frequent	Erythema during the course of radiotherapy; skin rashes, usually non- specific; exfoliative dermatitis; alopecia
	Frequency unknown	Urticaria; severe skin reactions sometimes fatal including toxic epidermal necrolysis/Stevens-Johnson syndrome; bullous dermatitis and drug reaction with eosinophilia and systematic symptoms
Musculoskeletal and connective tissue disorders	*Frequency unknown*	Lupus like syndrome
Reproductive system and breast disorders	*Less frequent*	Epididymo-orchitis; impotence
General disorders and administration site disorders	*Frequency unknown*	Granuloma, including bone marrow granuloma
Investigations	*Less frequent*	Increase in blood / serum creatinine

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 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 sinus bradycardia, heart block, attacks of ventricular tachycardia, Torsades de Pointes, circulatory failure, hepatic injury and conduction disturbances with the appearance of an idioventricular rhythm, particularly in the elderly patients or during digitalis therapy. In these circumstances MYORYTHM treatment should be withdrawn.

In the event of overdose treatment should be symptomatic, in addition to general supportive measures. The patient should be monitored and if bradycardia occurs beta-adrenostimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur.

Due to the pharmacokinetics of amiodarone, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended. Neither amiodarone nor its metabolites are dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A 6.2 Cardiac depressants.

ATC class: C01BD01 Anti-dysrhythmics, class III

Electro-physiological studies demonstrated that 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 atrioventricular 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 and the plasma half-life is usually of the order of 50 days. However there may be considerable inter-patient variation;

In individual patients a half-life of less than 20 days and a half-life of more than 100 days has been reported. High doses of amiodarone hydrochloride, for example 600 mg/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half-life of the medicine, a maintenance dose of only 200 mg/day, or less is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half-life is a valuable safeguard for patients with potentially lethal dysrhythmias as omission of occasional doses does not significantly influence the protection afforded by amiodarone hydrochloride.

There is a lack of conducted studies specifically focused on paediatric patients. However, based on the limited published data available for paediatric populations, there were no differences noted compared to adults.

Amiodarone is metabolised mainly by CYP3A4, and also by CYP2C8. Amiodarone and its metabolite, desethylamiodarone, exhibit a potential in vitro to inhibit CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4,CYP2A6, CYP2B6 and 2C8. Amiodarone and desethylamiodarone have also a potential to inhibit some transporters such as P-gp and organic cation transporter (OCT2). *In vivo* data describe amiodarone interactions on CYP3A4, CYP2C9, CYP2D6 and P-gp substrates.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate

Croscarmellose Sodium

Allura Red AC Aluminium Lake

Polysorbate 80

Povidone K-90

Pregelatinised Starch

Colloidal anhydrous silica

Purified Talc

Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packaging until required for use.

6.5 Nature and contents of container

Clear PVC/PVDC Aluminium blister strips in outer cardboard carton.

Pack size: 28 or 30 tablets.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8 REGISTRATION NUMBER

MYORYTHM 100: 56/6.2/0549

MYORYTHM 200: 56/6.2/0550

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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