PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

AZYRON 100 tablets

AZYRON 200 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg or 200 mg amiodarone hydrochloride.

Excipient with known effect:

Contains sugar: Lactose.

AZYRON 100 contains 35 mg lactose monohydrate per tablet.

AZYRON 200 contains 70 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

AZYRON 100: White to off-white, slightly speckled, round shaped, biconvex, uncoated tablets with break line on one side and plain on other side. Diameter is approximately 8,0 mm.

AZYRON 200: White to off-white, slightly speckled, round shaped, biconvex, uncoated tablets with break line on one side and plain on other side. Diameter is approximately 10,5 mm.

The tablets should be free of all physical defects.

The break line is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

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:

Treatment should be started with 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.

AZYRON 100 should be used to titrate the minimum dosage required to maintain control of the dysrhythmia. The maintenance dose should regularly be 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. AZYRON 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 AZYRON treatment withdrawn.

If AZYRON 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 elderly 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 employed. Particular attention should be paid to monitoring of thyroid function (see sections 4.3, 4.4 and 4.8).

Method of administration

AZYRON is for oral administration.

4.3 Contraindications

- AZYRON should not be administered to patients known to be allergic to amiodarone or any of the excipients (listed in section 6.1).
- Sinus bradycardia and sinoatrial heart block. In patients with severe conduction disturbances (high grade AV block, bifascicular or trifascicular block) or sinus node disease, AZYRON should only be used in conjunction with a pacemaker.
- Evidence or history of thyroid dysfunction. Thyroid function tests should be performed prior to and during therapy with AZYRON.
- Known hypersensitivity to iodine. AZYRON can induce erratic results from thyroid function tests. 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, AZYRON should be withdrawn. If necessary, beta-adrenostimulants or glucagon may be given.
- Pregnant or breastfeeding women.
- Safety and efficacy of AZYRON in paediatric patients have not been established.
- The concomitant use of medicines which may induce torsades de pointes (see section 4.5).

4.4 Special warnings and precautions for use

Due to substantial toxicity, AZYRON is intended for use only in patients with indicated life-threatening dysrhythmia. AZYRON has several potentially fatal toxicities of which the most important are pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis). Pulmonary toxicity has been fatal about 10 % of the time. Liver injury is common with AZYRON, but is usually mild and evidenced only by abnormal liver enzymes. Evident liver disease can occur, and has been fatal in a few cases. Like other antidysrhythmic medicine, AZYRON can exacerbate the dysrhythmia, e.g. by making the dysrhythmia less well tolerated or more difficult to reverse. This has occurred in 2 – 5 % of patients in various series, and significant heart block or sinus bradycardia has been seen in 2 – 5 %. Due to the long elimination half-life of AZYRON, the risk of proarrhythmic effects is prolonged after amiodarone is stopped.

Even in patients at high risk of dysrhythmic death, in whom the toxicity of AZYRON is an acceptable risk, AZYRON 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 AZYRON effectively and safely itself poses a significant risk to patients. Patients with the indicated dysrhythmia must be hospitalised while the loading dose of AZYRON 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 AZYRON with other medicines is made difficult by the unpredictable, changing amiodarone body burden.

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

AZYRON 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, AZYRON 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.

Treatment should be discontinued in case of onset of 2nd or 3rd degree AV block, sinoatrial block or bifascicular block.

Amiodarone has a low proarrhythmic 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 AZYRON, it is recommended to perform an ECG and serum potassium measurement. Monitoring of ECG is recommended during treatment.
AZYRON 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.

AZYRON should only be used in patients on sofosbuvir-containing regimen when other alternative antidysrhythmic 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 AZYRON 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 antidysrhythmic medicine as early as possible before transplant.

Endocrine disorders (see section 4.8):

Amiodarone may induce hypothyroidism or hyperthyroidism, particularly in patients with a personal history of thyroid disorders. Clinical and biological [including ultrasensitive TSH (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.

Amiodarone 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 amiodarone treatment, or, up to several months after discontinuation. Clinical features, such as weight loss, asthenia, restlessness, increase in heart rate, onset of dysrhythmia, angina and 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 antithyroid 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 AZYRON 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 AZYRON.

Nervous system disorders (see section 4.8):
AZYRON 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 AZYRON.

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 AZYRON can become unduly sensitive to sunlight, which may persist after several months of discontinuation of AZYRON. 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 including 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.

AZYRON contains lactose:

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

Use in elderly patients:

In elderly patients, heart rate may decrease markedly.

Paediatric patients:

Safety and efficacy of AZYRON in paediatric patients have not been established.

4.5 Interaction with other medicines and other forms of interaction

Medicines inducing torsades de pointes:

Combined therapy with the following medicines which prolong the QT interval is contraindicated (see section 4.3) due to the increased risk of torsades de pointes:

- Class Ia antidysrhythmic medicines, e.g. quinidine, procainamide, disopyramide.
- Class III antidysrhythmic medicines, e.g. sotalol, bretylium.
- Intravenous erythromycin, co-trimoxazole or pentamidine injection.
- Some antipsychotics, e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride and sertindole.
- Lithium and tricyclic antidepressants, e.g. doxepin, maprotiline, amitriptyline.
- Certain antihistamines, e.g. terfenadine, astemizole, mizolastine.
- Antimalarials, e.g. quinine, mefloquine, chloroquine, halofantrine.
- Concomitant use of AZYRON with fluoroquinolones (such as moxifloxacin) is contraindicated.
- Clarithromycin.

Medicines lowering heart rate or causing automaticity or conduction disorders:

Combined therapy with the following medicines 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.

Medicines which may induce hypokalaemia:

Combined therapy with the following medicines 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 with combined therapy with the following medicines which may also cause hypokalaemia and/or hypomagnesaemia, e.g. diuretics, systemic corticosteroids, tetracosactide, intravenous amphotericin.

In cases of hypokalaemia, corrective action should be taken and QT interval monitored. In case of torsades de pointes antidysrhythmic medicines should not be given; pacing may be instituted and IV magnesium may be used.

General anaesthetics:

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

Potentially serious complications have been reported when AZYRON is combined with general anaesthetics. These complications include: atropine resistant bradycardia, hypotension, conduction disturbances and a decrease in 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 AZYRON on other medicines

Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP1A1, CYP1A2, CYP3A4, CYP2C9, CYP2D6 and P-glycoprotein and may increase exposure of their substrates.
Due to the long half-life of amiodarone, interactions may be observed for several months after discontinuation of amiodarone.

P-gP substrates:

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

- *Digitalis:* Administration of AZYRON 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 AZYRON is coadministered with dabigatran due to the risk of bleeding. It may be necessary to adjust the dosage of dabigatran.

CYP2C9 substrates:

Amiodarone raises the plasma concentrations of oral anticoagulants (warfarin) and phenytoin by inhibition of CYP2C9:

- *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.

CYP3A4 substrates:

When such medicines are coadministered with AZYRON, 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 CYP3A4, such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolised by CYP3A4 when given with AZYRON.
- *Other medicines metabolised by CYP3A4:* Examples of such medicines are lidocaine (lignocaine), sirolimus, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine, ergotamine and colchicine.

CYP2D6 substrates:

- *Flecainide:* Given that flecainide is mainly metabolised by CYP2D6, 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.

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 CYP3A4 inhibitors during treatment with AZYRON.

Concomitant use of AZYRON and grapefruit juice should be avoided as the maximum plasma concentration of AZYRON is increased.

Other medicine interactions with amiodarone (see section 4.4):

- Coadministration of amiodarone 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

AZYRON is contraindicated in pregnancy and during lactation (see section 4.3).

Pregnancy:

There are insufficient data on the use of AZYRON during pregnancy in humans to judge any possible toxicity. However, in view of its effect on the fetal thyroid gland, AZYRON is contraindicated during pregnancy (see section 4.3).

Breastfeeding:

AZYRON is excreted into the breast milk in significant quantities and therefore breastfeeding is contraindicated (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 AZYRON 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: Angioneurotic oedema (Quincke's oedema), anaphylactic

shock/anaphylactoid reaction including shock.

Endocrine disorders

Frequent: Hyperthyroidism (sometimes fatal), hypothyroidism.

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

Metabolism and nutrition disorders

Frequency unknown: Decreased appetite.

Psychiatric disorders

Frequent: Libido decreased.

Frequency unknown: Confusional state, delirium, hallucination.

Nervous system disorders

Frequent: 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: Corneal micro-deposits 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 AZYRON.

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

Cardiac disorders

Frequent: Bradycardia (generally moderate and dose related).

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

Vascular disorders

Less frequent: Vasculitis.

Respiratory, thoracic and mediastinal disorders

Frequent: Hypersensitivity pneumonitis, pulmonary fibrosis or interstitial pneumonitis/alveolitis, pleuritis, 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).

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.

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 AZYRON is important. It allows continued monitoring of the benefit/risk balance of AZYRON. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

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 AZYRON should be withdrawn.

Treatment

The patients should be monitored and if bradycardia ensues 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.6.2 Cardiac depressants.

Pharmacotherapeutic group: Antiarrhythmics, class III.

ATC code: C01B D01.

Electrophysiological 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 (96 %) and the plasma half-life is usually approximately 50 days. However, there may be considerable inter-patient variation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Lactose monohydrate

Povidone

Magnesium stearate

Colloidal anhydrous silica

Sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C in a dry place. Protect from light.

Do not remove the blister strips from the carton until required for use.

6.5 Nature and contents of container

Alu/OPA/PVC blister strip containing 10 tablets each.

Or

Alu/PVC/PVDC blister strip containing 10 tablets each.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

AZYRON 100: 58/6.2/0099.097

AZYRON 200: 58/6.2/0100.098

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

20 August 2025

10. DATE OF REVISION OF THE TEXT

Not applicable.