PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

Hexarone® 100 (tablets)

Hexarone® 200 (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each HEXARONE 100 tablet contains 100 mg amiodarone hydrochloride.

Each HEXARONE 200 tablet contains 200 mg amiodarone hydrochloride.

Excipients with known effects:

Contains sugar (lactose monohydrate 48,00 mg per 100 mg tablet and 96,00 mg per 200 mg tablet).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

HEXARONE100: White, round tablets, one side scored, other side convex.

Diameter: 8,0 to 8,2 mm

HEXARONE 200: White, round tablets, biconvex with a one-sided score notch.

Diameter: 10,0 to 10,2 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of tachyarrhythmias associated with Wolff-Parkinson-White and other types of tachyarrhythmias 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

Adults:

The minimum effective dose should be used at all times. Dosage should be adjusted according to individual patient's response and well-being.

The following dosage regimen is generally effective:

Initial stabilization:

Initiate treatment with 200 mg three times daily for one week. Reduce this dosage to 200 mg twice daily for a further week.

Maintenance:

Following the initial stabilisation period, the dosage should be reduced to 200 mg daily, or less, if appropriate. The scored 100 mg tablet should be used to titrate the minimum dosage. The maintenance dose should be regularly reviewed, especially where this exceeds 200 mg daily.

General considerations:

It is necessary to administer high initial doses because the onset of action is slow, whilst the necessary tissue levels of amiodarone are being achieved.

Amiodarone has a very low acute toxicity; therefore, few serious problems have been observed during this initial phase.

Excessive dosing during maintenance therapy may cause side effects which are thought to be due to excessive tissue retention of amiodarone and / or it's metabolites.

The side effects gradually disappear as the tissue levels of amiodarone decline following reduction of dosage or withdrawal of amiodarone.

Once amiodarone treatment is withdrawn, residual tissue bound amiodarone may protect the patient for up to one month, but the likelihood of the reoccurrence of cardiac arrhythmias, during this period should be considered.

Patients should be regularly monitored for clinical signs of overdosage, and the dosage should be adjusted accordingly. It is most important that the minimum effective dose be used.

Use in the elderly:

It is important that the minimum effective dose be used.

Whilst there is no evidence that dosage requirements are different in the elderly, they may be more susceptible to bradycardia and conduction defects if too high a dose is administered. Particular attention should be paid to monitoring thyroid function, see section 4.3, 4.4 and 4.8

Method of administration

Oral

4.3 Contraindications

Known hypersensitivity to iodine or to amiodarone or to any of the excipients (see section 6.1).

- Sinus bradycardia (less than 55 pulse beats per minute) and sino-atrial heart block.

  In patients with severe conduction disturbances (high grade AV-blocks of second

and third degrees as well as bifascicular and trifascicular block) or sinus node disease, HEXARONE should be used only in conjunction with a pacemaker.

- Where there is evidence or history of thyroid dysfunction. A thyroid function test should be performed prior to therapy in all patients.

- Pre-existing QT prolongation.

  The combination of HEXARONE with medicines which may prolong the QT interval and thereby induce torsades de pointes ventricular tachycardia is contraindicated (see section 4.5).

- HEXARONE should not be given to patients with hypokalaemia.
- Concomitant treatment with monoamine oxidase (MOA) inhibitors is contraindicated.
- HEXARONE is contraindicated in patients with severe respiratory failure.
- HEXARONE is contraindicated during pregnancy and lactation.

4.4 Special warnings and precautions for use

HEXARONE 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.

Anaesthesia

Caution is advised in patients undergoing general anaesthesia, also in patients receiving high-dose oxygen therapy. Before surgery, the anaesthetist should be informed that the patient is taking HEXARONE, see section 4.5 and 4.8.

Cardiac disorders

Too high a dose of HEXARONE may lead to severe bradycardia and to conduction disturbances with the appearance of idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances therapy should be withdrawn. If necessary, beta adrenostimulants or glucagon may be given. If bradycardia is severe and symptomatic, the insertion of a pacemaker should be considered due to the long half-life of amiodarone, see section 4.8.

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

In patients taking HEXARONE, QT interval lengthening has been seen, corresponding to prolonged repolarization with the possible development of U-waves and deformed T-waves. There is an increased risk of “torsades de pointes” in case of an excessive QT prolongation. These changes are evidence of its pharmacological action and do not reflect toxicity. In the elderly heart rate may decrease markedly.

Treatment should be discontinued in the case of onset of second or third-degree AV block, sino-atrial block, or bifascicular block. Before starting HEXARONE, it is recommended that an ECG be performed, and serum potassium levels be assessed. Monitoring of ECG is recommended throughout treatment (e.g., standard ECG at intervals of one month or long-term ECG at intervals of three months and if appropriate stress ECG). The therapy should

be re-evaluated, if a deterioration of individual parameters, such as extension of the QRS or QT interval by more than 25 % or of the PQ time by more than 50 % and QT prolongation to more than 500 ms or an increase in the number and severity of arrhythmia occurs.

HEXARONE has a low proarrhythmic effect. Onsets of new arrhythmias or worsening of treated arrhythmias has been observed with sometimes a fatal outcome. It is important, but difficult, to determine if this effect is due to a lack of efficacy of the medicine from a proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects generally occur in the context of QT prolonging factors, such as medicine interactions and/or electrolyte disorders, see section 4.5 and 4.8. Despite QT interval prolongation, HEXARONE exhibits a low torsadogenic activity.

HEXARONE 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

Cases of severe, potentially life-threatening bradycardia and heart block have been observed when HEXARONE is used in combination with sofosbuvir in combination with another hepatitis C virus (HCV) direct acting antiviral (DAA), such as daclatasvir, simeprevir, or ledipasvir. Therefore, coadministration of these medicines with amiodarone is not recommended.

If concomitant use with HEXARONE cannot be avoided, it is recommended that patients are closely monitored when initiating sofosbuvir in combination with other DAAs. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored

for at least 48 hours in an appropriate clinical setting after initiation of the concomitant treatment with sofosbuvir.

Patients receiving these hepatitis C medicines with HEXARONE, with or without other medicines that lower heart rate, should be warned of the symptoms of bradycardia and heart block and should be advised to seek urgent medical advice if they experience them, see section 4.5

Hepatobiliary disorders

HEXARONE may be associated with a variety of hepatic effects, including cirrhosis, hepatitis, jaundice and hepatic failure. In some cases, particularly following long-term therapy, the outcome of these effects has been fatal, although rarely they have occurred soon after starting treatment particularly after amiodarone intravenous (with intravenous application already during the first 24 hours). It is advisable to monitor liver function, particularly transaminases, before treatment and 6-monthly thereafter. Regular checks of liver function should be performed during therapy. HEXARONE dose should be reduced, or the treatment discontinued if the transaminases increase exceeds 3 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 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, see section 4.8

There have been no literature reports on the potentiation of hepatic adverse effects of alcohol; however, patients should be advised to moderate their alcohol intake while taking HEXARONE.

Eye disorders

If blurred or decreased vision occurs, complete ophthalmologic examination, including funduscopy and slit-lamp examinations should be promptly performed. Appearance of optic neuropathy and/or optic neuritis requires HEXARONE withdrawal due to the potential progression to blindness. Unless blurred or decreased vision occurs, ophthalmological examination recommended annually, see section 4.8

Respiratory, thoracic and mediastinal disorders

Patients should be carefully evaluated clinically, and consideration given to chest X-rays before starting therapy. Of particular concern with patients taking HEXARONE is pulmonary toxicity, the symptoms of which include dyspnoea (which may be severe and unexplained by the current cardiac status), non-productive cough, and deterioration of 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. Pulmonary toxicity may also present as pulmonary fibrosis, pleuritis or pneumonitis, including hypersensitivity, alveolar, interstitial, or bronchiolitis obliterans organising pneumonitis.

Therefore, thoracic roentgenography and pulmonary function test should be performed prior to the onset of treatment. These examinations should be repeated at intervals of approximately 3-6 months in the further therapeutic course. These examinations should also be carried out if dyspnoea (symptom of a possible pulmotoxic effect) occurs, see section 4.8

In patients with severe lung disease, pulmonary function is to be monitored more frequently, as these patients have a worsened prognosis if pulmotoxic effects occur.

By proof of hypersensitivity pneumonitis, HEXARONE is to be withdrawn immediately and therapy with corticosteroids initiated.

By proof of alveolar/interstitial pneumonia, treatment should be carried out with corticosteroids and the dose reduced or - if possible - amiodarone should be discontinued.

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. However, some patients can deteriorate despite discontinuing amiodarone.

Very rare cases of severe, in some cases fatal, respiratory complications (acute respiratory distress syndrome), usually right after surgical interventions have been reported, see also section 4.5.

Endocrine disorders

HEXARONE may induce hyperthyroidism or hypothyroidism, particularly in patients with a personal history of thyroid disorders. Clinical and biological monitoring (including

ultrasensitive TSH (usTSH)) should be performed prior to therapy in all patients. Monitoring should be carried out during treatment at 6-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.

HEXARONE contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function test (free-T_3, free-T_4, usTSH) remain interpretable. HEXARONE 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 HEXARONE treatment if there is no clinical or further biological (usTSH) evidence of thyroid disease, see section 4.8

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, normalisation of the thyroid function occurs usually within 1 to 3 months. In life-threatening situations, HEXARONE therapy can be continued in combination with levothyroxine. The dose of levothyroxine is adjusted according to TSH levels. In individual cases, a discontinuation of HEXARONE may be required.

On account of its iodine content, HEXARONE falsifies classic thyroid tests (iodine binding test).

Hyperthyroidism

Hyperthyroidism may occur during HEXARONE treatment, or up to several months after discontinuation. Clinical features, such as weight loss, tachycardia, tremor, nervousness, increased sweating, heat intolerance, asthenia, restlessness, increase in heart rate, onset of arrhythmia, angina pectoris, congestive heart failure should alert the physician. The diagnosis is supported by a decrease in serum usTSH level, and elevated T_3 and T_4 values, 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.

Nervous system disorders

HEXARONE may induce peripheral sensorimotor neuropathy and/or myopathy. Both these conditions may be severe, although recovery usually occurs within several months after HEXARONE withdrawal; such recoveries may sometimes, however, be incomplete, see section 4.8

Skin and subcutaneous tissue disorders

Hypersensitivity to sunlight may occur, which may persist after several months of discontinuation of HEXARONE and patients taking HEXARONE should be instructed to avoid exposure to sun, this also applies to UV light applications and solar or if unavoidable to use adequate protection. Even after withdrawal of HEXARONE, a light protector is necessary for some more time. In most cases symptoms are limited to tingling, burning and erythema of sun-exposed skin but severe phototoxic reactions with blistering may be seen, see section 4.8

Medicine interactions

Concomitant use of HEXARONE is not recommended with the following medicines: beta-blockers, heart rate lowering calcium channel blockers with antiarrhythmic effect (verapamil, diltiazem), stimulant laxatives, which may cause hypokalaemia.

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

Amiodarone is an inhibitor of cytochrome P450 3A4. Therefore, statins that are metabolised by CYP 3A4 (e.g., simvastatin, atorvastatin, lovastatin) should not be used concomitantly with HEXARONE, see section 4.5

Porphyria

Avoid the use of HEXARONE in patients suffering from porphyria.

Important information about some excipients

Hexarone tablets contains lactose anhydrous, which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take HEXARONE tablets.

4.5 Interaction with other medicines and other forms of interaction

Some of the more important medicines that interact with HEXARONE include warfarin, digoxin, phenytoin, fluoroquinolones and any medicines which prolong the QT interval.

Amiodarone raises the plasma concentrations of oral anticoagulants and phenytoin, and any other highly protein bound medicines, through inhibition of CYP 2C9. The dose of warfarin should be reduced accordingly. More frequent monitoring of prothrombin time both during and after HEXARONE treatment is recommended. Phenytoin dosage should be reduced if signs of overdosage appear, and plasma levels may be measured.

In patients already receiving digoxin, the subsequent administration of amiodarone will increase their plasma digoxin concentration levels, resulting in signs and symptoms associated with high levels of digoxin. Clinical, ECG and biological monitoring and a reduction of digoxin dosage by half are recommended. A synergistic effect on heart rate and atrioventricular conduction is also possible.

Pharmacodynamic interactions

Medicines inducing Torsade de Pointes or prolonging QT:

Medicines inducing Torsade de Pointes:

Combined therapy with any medicine known to prolong the QT interval is contraindicated (see section 4.3) due to the increased risk of torsades de pointes. They include the following:

- Class Ia anti-arrhythmic medicines e.g., quinidine, procainamide, disopyramide

- Class III anti-arrhythmic medicines 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
- Anti-malarials e.g., quinine, mefloquine, chloroquine, halofantrine
- Moxifloxacin

Medicines prolonging QT interval:

Co-administration of HEXARONE with medicines 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 HEXARONE with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contraindicated). There have been rare reports of QTc interval prolongation, with or without torsades de pointes, in patients taking HEXARONE with fluoroquinolones, see section 4.3

Medicines lowering heart rate or causing automaticity or conduction disorders:

Combined therapy with the following substances is not recommended:

Beta blockers and certain 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 substances 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 medicines which may cause hypokalaemia and/or hypomagnesaemia, e.g., diuretics, systemic corticosteroids, tetracosactide, intravenous amphotericin.

In the case of hypokalaemia, corrective action should be taken, and QT interval monitored.

In the case of torsades de pointes antiarrhythmic agents should not be given; pacing may be instituted, and IV magnesium may be used.

General anaesthesia:

Caution is advised also in patients undergoing general anaesthesia or receiving high dose oxygen therapy. The anaesthetist should always be informed that the patient is taking HEXARONE.

Potentially severe complications have been reported in patients taking HEXARONE undergoing general anaesthesia, such as 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 amiodarone on other medicines:

Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP 1A1, CYP 1A2, CYP

3A4, CYP 2C9, CYP 2D6 and P-glycoprotein and may increase exposure of their substrates. Due to the long half-life of amiodarone, interactions may be observed for several months after discontinuation of HEXARONE.

P-gP substrates:

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

Digitalis:

Administration of HEXARONE 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 dose should be halved. A synergistic effect on heart rate and atrioventricular conduction is also possible.

Dabigatran:

Caution should be exercised when HEXARONE is co-administered with dabigatran due to the risk of bleeding. It may be necessary to adjust the dose of dabigatran as per its label.

CYP 2C9 substrates:

Amiodarone raises the plasma concentrations of oral anticoagulants (e.g., 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 HEXARONE treatment is recommended.

Phenytoin:

Phenytoin dose should be reduced if signs of overdose appear (resulting in neurological signs), and plasma levels may be measured.

CYP P450 3A4 substrates:

When such substances are co-administered with HEXARONE, 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.

Fentanyl:

HEXARONE may potentiate the pharmacological effects of fentanyl and thus may increase the risk of toxic effects.

Statins:

The risk of muscular toxicity is increased by concomitant administration of HEXARONE 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 HEXARONE.

Other substances metabolised by cytochrome P450 3A4:

Examples of such medicines are lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine, ergotamine and colchicine.

CYP 2D6 substrates:

Flecainide:

Given that flecainide is mainly metabolised by CYP 2D6, by inhibiting this isoenzyme, HEXARONE 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 products on HEXARONE:

CYP 3A4 inhibitors and CYP 2C8 inhibitors may have a potential to inhibit HEXARONE metabolism and to increase its exposure.

It is recommended to avoid CYP 3A4 inhibitors during treatment with HEXARONE. Grapefruit juice inhibits cytochrome P450 3A4 and may increase the plasma concentration of amiodarone. Grapefruit juice should be avoided during treatment with oral HEXARONE.

Other medicine interactions with amiodarone

Co-administration of amiodarone with sofosbuvir in combination with another HCV direct acting antiviral (such as daclatasvir, simeprevir, or ledipasvir) is not recommended as it may lead to serious symptomatic bradycardia. The mechanism of this bradycardia effect is unknown.

If co-administration cannot be avoided, cardiac monitoring is recommended, see section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

Amiodarone has harmful pharmacological effects on pregnancy, the foetus and the

newborn. Amiodarone and N-demethyl amiodarone pass the placenta and reach concentrations in the child of 10 to 25 % of the maternal plasma concentration. Growth disturbances, preterm birth and thyroid dysfunctions in the neonate are the most frequent complications. Hypothyroidism, bradycardia and prolonged QT intervals have been ascertained in approximately 10 % of neonates. In isolated cases, thyroid enlargement or cardiac murmur have been found. The malformation rate does not seem to be increased. However, the possibility of cardiac defects should be taken into consideration.

HEXARONE must not be used during pregnancy.

Women who want to conceive should plan the beginning of a pregnancy six months after ending therapy at the earliest in order to avoid any exposure of the child in early pregnancy.

Lactation

Amiodarone is excreted into the breast milk in significant quantities and breastfeeding is contraindicated.

4.7 Effects on ability to drive and use machines

Treatment with this medicine requires regular medical monitoring. Even when this medicine is used according to the instructions, reactivity may be changed in such a way that the ability to drive, to operate machinery or to work in an unsafe posture is impaired.

This applies to a higher extent at the onset of therapy, when increasing the dose and changing the preparation as well as in combination with alcohol and in patients with clinical symptoms of amiodarone-induced eye disorders.

4.8 Undesirable effects

The evaluation of side effects is based on the following information on frequencies:

Frequent: (≥ 1/10), (≥ 1/100 up to < 1/10)

Less frequent: (≥ 1/1 000 up to < 1/100), (≥ 1/10 000 up to < 1/1 000), (< 1/10 000)

Frequency unknown: cannot be estimated from the available data

Due to possible serious adverse reactions affecting the lung, liver, thyroid gland, skin and peripheral nervous system, patients on long-term amiodarone treatment should be carefully supervised. These reactions can also be delayed.

Blood and lymphatic system disorders:

Less frequent: Thrombocytopenia, haemolytic anaemia, aplastic anaemia, 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: Hypothyroidism, hyperthyroidism (sometimes fatal).

Less frequent: Syndrome of inappropriate antidiuretic hormone secretion (SIADH), see section 4.4.

Metabolism and nutrition disorders:

Frequency unknown: Decreased appetite.

Psychiatric disorders:

Frequent: Decreased libido.

Less frequent: Hallucinations.

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 sensimotor neuropathy and/or myopathy, usually reversible after discontinuation of treatment (see section 4.4), vertigo, benign intracranial hypertension (pseudo-tumour cerebri), cerebral ataxia (for which regression usually occurs after reduction of dose or withdrawal), headache.

Frequency unknown: Parkinsonism, parosmia.

Eye disorders:

Frequent: Corneal microdeposits (can also be described as Cornea verticillata) usually limited to the area under the pupil, which are usually only discernible by slit-lamp examinations. They may be associated with coloured halos in dazzling light or blurred vision. Corneal microdeposits consist of complex lipid deposits and are reversible within 6 to 12 months following discontinuation of treatment. The deposits are considered essentially benign and do not require discontinuation of HEXARONE.

Less frequent: Optic neuropathy and/or optic neuritis that may progress to blindness, see section 4.4.

Cardiac disorders:

Frequent: Bradycardia (generally moderate and dose related).

Less frequent: Onset or worsening of arrhythmia, sometimes followed by cardiac arrest, see

section 4.4 and 4.5. Conduction disturbances (sinoatrial block, AV block of various degrees), see section 4.4; in individual cases asystole was observed (see section 4.4). Marked bradycardia or sinus arrest in patients with sinus node dysfunction and/or in elderly patients.
Frequency unknown: Torsades des pointes, see section 4.4 and 4.5.

Individual cases of ventricular fibrillation flutter have been described, see section 4.4 concerning follow-up examinations, diagnostic and therapeutic measures).

Vascular disorders:

Less frequent: Vasculitis.

Respiratory, thoracic and mediastinal disorders:

Frequent: Pulmonary toxicity (hypersensitivity pneumonitis, alveolar or interstitial pneumonitis or fibroses, pleuritis, bronchiolitis obliterans organising pneumonia/BOOP), sometimes fatal, see section 4.4.
Non-productive cough and dyspnoea are often first signs of the pulmonary alterations mentioned above. Furthermore, weight loss, fever, asthenia may occur.
Less frequent: Bronchospasm in patients with severe respiratory failure and especially in asthmatic patients. Pulmonary haemorrhage. Cases of shock lung (ARDS) occurred mostly after surgery, in individual cases with fatal outcome (possible interaction with a high oxygen concentration, see sections 4.4 and 4.5).

(For follow-up examinations, diagnostic and therapeutic measures, see section 4.4).

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.

Hepatobiliary disorders

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.

(For follow-up examinations, diagnostic and therapeutic measures, see section 4.4).

Skin and subcutaneous tissue disorders:

Frequent: Photosensitivity with increased tendency to sunburns, which can lead to erythema and rash. Slate-grey or bluish pigmentations of light-exposed skin (pseudocyanosis) particularly the face, in case of prolonged treatment with high daily dosages; such pigmentation slowly disappears within 1 to 4 years following treatment discontinuation (see section 4.4). Eczema.

Less frequent: Erythema during the course of radiation therapy, erythema nodosum, skin rashes, usually non-specific, exfoliative dermatitis, alopecia.

Frequency unknown: Urticaria, severe skin reactions such as toxic epidermal necrolysis (TEN) / Stevens-Johnson syndrome (SJS), bullous dermatitis and drug reaction with eosinophilia and systemic symptoms (DRESS).

(For preventive measures, see section 4.4).

Musculoskeletal and connective tissue disorders

Frequent: Muscle weakness.

Frequency unknown: Lupus like syndrome.

Reproductive system and breast disorders:

Less frequent: Epididymo-orchitis, impotence.

General disorders and administration site disorders:

Less frequent: Fatigue.

Frequency unknown: Granuloma*,* including bone marrow granuloma.

***Investigations*:**

Less frequent: Increase in blood 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

Suspected adverse reactions can also be reported directly to the HCR via https://pvi1.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

Little information is available regarding acute overdosage with oral amiodarone. Few cases of sinus bradycardia, heart block, attacks of ventricular tachycardia, Torsades de Pointes, circulatory failure and hepatic injury have been reported, particularly in elderly patients or during digitalis therapy. In these circumstances amiodarone therapy should be withdrawn.

In the event of an overdose, treatment should be symptomatic; gastric lavage may be employed to reduce absorption, in addition to general supportive measures. Patients 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 (long half-life), adequate and prolonged surveillance of the patient, particularly cardiac status is recommended. Neither amiodarone nor its metabolites are dialyzable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A.6.2. Cardiac suppressants

5.1 Pharmacodynamic properties

Amiodarone is predominantly a class III antiarrhythmic agent.

Amiodarone prolongs the duration of the action potential, particularly in the nodal and Purkinje tissue.

Amiodarone does not seem 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 pathways.

The conduction rate is reduced in the atria, UV node and accessory pathways.

Amiodarone also exhibits non-competitive alpha and beta adrenoreceptor antagonism.

5.2 Pharmacokinetic properties

Amiodarone is strongly protein bound and has an average plasma half-life 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 initial doses of amiodarone, for example 600 mg/day, should be given 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 new distribution equilibrium to be achieved between dose adjustments.

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

No controlled paediatric studies have been undertaken. In the limited published data available in paediatric patients, there were no differences noted compared to adults.

Amiodarone is metabolised mainly by CYP 3A4, and also by CYP 2C8. Amiodarone and its metabolite, desethylamiodarone, exhibit a potential *in vitro* to inhibit CYP 1A1, CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, CYP 3A4, CYP 2A6, CYP 2B6 and CYP 2C8. Amiodarone and desethylamiodarone have also a potential to inhibit some transporters such as P-gp and organic cation transporter (OCT2) (one study shows a 1,1 % increase in concentration of creatine (a OCT2 substrate). *In vivo* data describe amiodarone interactions on CYP 3A4, CYP 2C9, CYP 2D6 and P-gp substrates.

5.3 Preclinical safety data

In a 2-year carcinogenicity study in rats, amiodarone caused an increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinical relevant exposures. Since mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is

proposed for this type of tumour induction. In the mouse, carcinomas were not observed, but a dose-dependent thyroid follicular hyperplasia was seen. These effects on the thyroid in rats and mice are most likely due to effects of amiodarone on the synthesis and/or release of thyroid gland hormones. The relevance of these findings to man is low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients are anhydrous colloidal silica, lactose monohydrate, magnesium stearate, maize starch and polyvidone 25.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

White, opaque PP/Aluminium blisters.

Packs of 30’s.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei view

Midrand

2090

8. REGISTRATION NUMBER(S)

HEXARONE® 100: 32/6.2/0650

HEXARONE® 200: 32/6.2/0651

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 February 2000

10. DATE OF REVISION OF THE TEXT

30 November 2022

Additional countries registration details:

Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Hexarone 100	S2	BOT1202208
	Hexarone 200	S2	BOT1202113
Namibia	Hexarone 100	NS2	04/6.2/1337
	Hexarone 200	NS2	04/6.2/1338

ATC code: C01BD01 – Antiarrhythmics, class III

Name and address of manufacturer:

Salutas Pharma GmbH

Otto-von Guericke-Allee 1

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Germany

[1]Company Reg. No.: 1990/001979/07