AMIOHEXAL 200 TABLET

Each **Amiohexal 200 Tablet** contains Amiodarone HCl 200 mg.

DESCRIPTION
White, round tablets, biconvex with one-sided score notch.

INDICATIONS
- Symptomatic and tachycardiac supraventricular disturbances of heart rhythm such as AV-junctional tachycardias, supraventricular tachycardias associated with Wolff-Parkinson-White syndrome or paroxysmal atrial fibrillation when other drugs cannot be used.
- Severe symptomatic ventricular tachycardiac ventricular disturbances of heart rhythm.

RECOMMENDED DOSAGE
Amiohexal 200 is a highly toxic drug; therefore the lowest effective dosage should be used so as to minimise the risk and occurrence of adverse effects. Dosage of amiodarone hydrochloride must be carefully adjusted according to individual requirements and response, patient tolerance, and the general condition and cardiovascular status of the patient. Clinical and ECG monitoring of cardiac function, is recommended during therapy with the drug. When dosage adjustment is necessary, the patient should be monitored closely for an extended period of time because of the long and variable elimination half-life of amiodarone and the difficulty in predicting the length of time required to attain a new steady-state plasma concentration of the drug.

Loading dose: 600 mg amiodarone (corresponding to 3 tablets of **Amiohexal 200**) per day for 8-10 days; in some cases, dosages of up to 1200 mg amiodarone (corresponding to 6 tablets of **Amiohexal 200**) may be required per day. The dosage is then reduced gradually to maintenance dose. It is recommended to perform loading-dose phase of therapy in a hospital setting.

Maintenance dose: Usually 200 mg amiodarone (corresponding to 1 tablet of **Amiohexal 200**) per day for 5 days per week, with a pause of 2 days, and this is possible due to prolonged half-life of amiodarone. **Amiohexal 200** may also be given on every second day (1 tablet of **Amiohexal 200** may be given on every second day when a dose of 100 mg daily is recommended).

In some cases, higher dosages of 200-600 mg amiodarone (corresponding to 1-3 tablets of **Amiohexal 200**) per day are required during long term therapy.

Paediatric population
The safety and efficacy of amiodarone in children has not been established.

Elderly
Amiohexal 200 causes a deceleration in the heart frequency, which can be more pronounced in elderly patients. Therapy must be discontinued in cases of pronounced deceleration of the heart frequency.

ROUTE OF ADMINISTRATION
For oral administration.

CONTRAINDICATIONS
Amiohexal 200 is contraindicated in the following cases:

- Hypersensitivity to amiodarone or to any of the excipients;
- Sinus bradycardia (less than 55 pulse beats per minute);
- All forms of delayed conduction (sinuauricular and nodal conduction delay) including sick sinus node syndrome, AV blocks of second and third degrees as well as bifascicular and trifascicular blocks unless a pacemaker is used;
- Disease of thyroid gland;
- Pre-existing QT prolongation;
- Hypokalaemia;
- Allergy to iodine;
- Concomitant treatment with MAO inhibitors;
- Concomitant treatment with medicinal products which may induce "*torsades de pointes*";
- During pregnancy, unless clearly indicated (see *Pregnancy and Lactation*);
- During lactation (see *Pregnancy and Lactation*).

WARNINGS AND PRECAUTIONS

Before starting treatment, it is recommended to check the cardiac function (ECG), the serum potassium value, liver values, the thyroid and lung function and to perform a chest X-ray.

Cardiovascular system (see *Side Effects)*

ECG alterations, imposing as QT prolongation (in dependence of prolonged repolarisation) possibly in connection with the development of a U-wave as well as prolongation and deformation of the T-wave, demonstrate the pharmacological activity of **Amiohexal 200.** There is an increased risk of *torsades de pointes* in case of an excessive QT prolongation.

As a consequence of the pharmacological action of **Amiohexal 200** sinus bradycardia which may be more pronounced in elderly patients or in case of an impaired sinus node function may occur. In exceptional cases sinus node arrest may develop.

If pronounced bradycardia or sinus node arrest occurs, the treatment must be discontinued.

Proarrhythmic effects in the form of new or enhanced cardiac arrhythmia that can be life-threatening have been described.

It is important, but difficult to differentiate a lack of efficacy of the medicinal product from a proarrhythmic effect. Proarrhythmic effects during treatment with **Amiohexal 200** mainly occur in connection with QT-prolonging factors, such as drug interactions and/or electrolyte imbalance (see *Drug Interactions* and *Side Effects*). Despite QT prolongation **Amiohexal 200** shows a low torsadogenic activity.

Cases have been described, especially with the chronic use of antiarrhythmic substances, in which the threshold for ventricular defibrillation and/or pacing of pacemakers or implantable cardioverter-defibrillators was increased. Thus, the function of the devices could potentially be affected. Therefore, it is recommended to repeatedly check the functionality of the devices before and during amiodarone therapy.

Cardiologic check-ups should be performed during treatment at regular intervals (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.

Severe bradycardia (see *Drug Interactions*)

Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone 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, co-administration of these agents with amiodarone is not recommended.

If concomitant use with amiodarone cannot be avoided, it is recommended that patients are closely monitored when initiating sofosbuvir in combination with other DAAs. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for at least 48 hours in an appropriate clinical setting after initiation of the concomitant treatment with sofosbuvir.

Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofosbuvir in combination with other DAAs.

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

Endocrine disorders (see *Side Effects)*
Due to the risk of developing a thyroid dysfunction (hyperthyroidism or hypothyroidism) on treatment with **Amiohexal 200**, thyroid function should be examined prior to the onset of treatment. During therapy and up to one year after its withdrawing, these examinations should be repeated at regular intervals and the patients examined for clinical symptoms of hyperthyroidism or hypothyroidism.

Amiohexal 200 inhibits the transformation of thyroxine (T_4) into triiodothyronine (T_3) and may lead to increased T_4 values as well as to decreased T_3 values in clinically inconspicuous (euthyroid) patients. This findings constellation alone should not result in discontinuing therapy.

The following symptoms can be signs of hypothyroidism:
Weight gain, cold intolerance, fatigue, extreme bradycardia that exceeds the effect expected with **Amiohexal 200**.
The clinical diagnosis of hypothyroidism is confirmed by proof of evidently increased ultrasensitive TSH as well as decreased T_4 values. After discontinuation of treatment, normalization of the thyroid function occurs usually within 1-3 months.
The **Amiohexal 200** dose should - if possible - be reduced and/or substitution with levothyroxine be started if hypothyroidism is detected. In individual cases, a discontinuation of **Amiohexal 200** may be required.

Hyperthyroidism may occur during therapy or up to several months after discontinuation of amiodarone therapy. The following, usually mild symptoms should be considered by the physician: Weight loss, tachycardia, tremor, nervousness, increased sweating and heat intolerance, recurrence of arrhythmia or angina pectoris, heart failure. Amiodarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of arrhythmia breakthrough or aggravation. In fact, IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED.

The clinical diagnosis of hyperthyroidism is confirmed by proof of evidently decreased ultrasensitive TSH as well as increased T_3 and T_4 values. In the case of hyperthyroidism, therapy should be withdrawn. Improvement occurs within several months after discontinuation of treatment and is accompanied by a normalization of the thyroid function test.
In severe cases (sometimes fatal) an individual emergency treatment with antithyroid drugs,

beta-blockers and/or corticosteroids has to be started.
On account of its iodine content, **Amiohexal 200** falsifies classic thyroid tests (iodine binding test).

Skin
During therapy with **Amiohexal 200**, exposure to sunlight should be avoided; this also applies to UV light applications and solaria. If this is not possible, uncovered skin areas, particularly the face, should be protected by application of an ointment with a high protection factor. Even after withdrawal of **Amiohexal 200**, a light protector is necessary for some more time.
During long-term treatment, a blue-grey discoloration of the exposed skin may occur. The risk may be increased in patients of fair complexion or those with excessive sun exposure and may be related to cumulative dose and duration of therapy.

Severe bullous skin reaction (see *Side Effects*)
Life-threatening or even fatal skin reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). If symptoms or signs of SJS, TEN are present (such as progressive skin rash, often with blisters or mucosal lesions), **Amiohexal 200** must be discontinued immediately.

Lung (see *Side Effects*)
During therapy with **Amiohexal 200**, there is the risk of developing severe inflammatory pneumopathy (hypersensitivity pneumonitis, alveolar or interstitial pneumonitis). Non-productive cough and dyspnoea are common symptoms of the above mentioned pulmonary changes. Furthermore, weight loss, fever, weakness may occur.
Therefore, baseline chest X-ray and pulmonary function tests, including diffusion capacity, should be performed prior to the onset of treatment. These examinations should be repeated at intervals of approximately 3-6 months in further therapeutic courses.
These examinations should also be carried out if dyspnoea (symptom of a possible pulmotoxic effect) occurs.
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, **Amiohexal 200** is to be withdrawn immediately and therapy with corticosteroids initiated.
By proof of an alveolar/interstitial pneumonitis, treatment should be carried out with corticosteroids and the dose reduced or - if possible - **Amiohexal 200** be discontinued. If **Amiohexal 200** is withdrawn early, interstitial pneumonia usually recedes.
Very rare cases of severe, in some cases fatal, respiratory complications (acute respiratory distress syndrome, ADRS), usually right after surgical interventions have been reported (see *Drug Interactions*).

Liver (see *Side Effects*)
Monitoring of liver enzymes (transaminases) based on liver function tests is recommended once amiodarone therapy is started. Regular checks of liver function should be performed during therapy.
Acute liver disease (including severe hepatocellular insufficiency or liver failure, in some cases with fatal outcome) and chronic liver disease can occur with the oral and intravenous dosage form of **Amiohexal 200** (with intravenous application already during the first 24 hours). Therefore, the dose should be reduced or **Amiohexal 200** discontinued if transaminase levels increase to values exceeding 3 times the norm.
The clinical and laboratory signs of chronic liver disease due to oral amiodarone therapy may be minimal (cholestatic jaundice, hepatomegaly, transaminases increased to up to 5 times the norm). Liver dysfunction is reversible after discontinuation of **Amiohexal 200**, but cases with fatal outcome have been reported.

Neuromuscular disorders (see *Side Effects*)
Amiodarone can cause peripheral neuropathy and/or myopathy. These usually disappear a few months after discontinuation of **Amiohexal 200**, but may not be completely reversible in some cases.

Eye (see *Side Effects*)
Regular ophthalmological investigations, including funduscopy and slit-lamp examinations have to be performed during treatment with amiodarone. 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.

Medicinal product interactions (see *Drug Interactions*)
The concomitant use of **Amiohexal 200** with the following medicinal products is not recommended: Beta-blockers, calcium channel blockers with antiarrhythmic effect (verapamil, diltiazem), laxatives which can cause hypokalaemia.
Amiodarone is an inhibitor of cytochrome P450 (CYP) 3A4. Therefore statins that are metabolized by CYP3A4 (e.g. simvastatin, atorvastatin, lovastatin) should not be used concomitantly with **Amiohexal 200**.

Electrolyte Disturbances
Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in patients with hypokalaemia, any electrolyte disorders e.g. potassium or magnesium deficiency should be corrected before instituting amiodarone therapy.

Surgery
Hypotension Postbypass: Rare occurrences of hypotension upon discontinuation of cardiopulmonary bypass during open-heart surgery in patients receiving amiodarone have been reported. Atropine- resistant sinus bradycardia, sinus arrest and/or AV block also have occurred in some patients undergoing general anaesthesia for major surgery. The relationship of this event to amiodarone therapy is unknown. Prior to surgery, the anaesthesiologist should be informed about the amiodarone therapy.

Transplantation
In retrospective studies, amiodarone use in the transplant recipient prior to heart transplant has been associated with an increased risk of primary graft dysfunction (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 *Side Effects*). Severe PGD may be irreversible.

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

Effects on Ability to Drive and Use Machine
Treatment with this medicinal product requires regular medical monitoring. Even when this medicinal product 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.

DRUG INTERACTIONS

Pharmacodynamic interactions

Medicinal products inducing torsade de pointes or prolonging QT

Medicinal products inducing *torsade de pointes*

Combined therapy with the following drugs which prolong the QT interval is contraindicated (see *Contraindications*) due to the increased risk of *torsades de pointes*; for example:

- Class Ia anti-arrhythmic drugs e.g. quinidine, procainamide, disopyramide
- Class III anti-arrhythmic drugs 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
- Methadone

Medicinal products prolonging QT interval

Co-administration of **Amiohexal 200** with drug 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 **Amiohexal 200** 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 **Amiohexal 200** with fluoroquinolones.

Medicinal products lowering heart rate or causing automaticity or conduction disorders

Combined therapy with the following drugs is not recommended:

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

Agents 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 drugs 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* antiarrhythmic agents 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 severe complications have been reported in patients taking amiodarone 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 amiodarone on other medicinal products

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. Co-administration with P-gP substrates is expected to result in an increase of their exposure:

Digitalis

Administration of amiodarone 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 amiodarone 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.

CYP2C9 substrates

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

Warfarin

An increase in prothrombin time (PT) appears to occur in almost all patients treated with **Amiohexal 200** and a coumarin or indandione anticoagulant (e.g., warfarin) concomitantly and this can result in serious or fatal haemorrhage. Therefore if **Amiohexal 200** therapy is initiated, the dose of the anticoagulant should be reduced accordingly. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended.

Phenytoin

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

CYP3A4 substrates

When such substances are co-administered with amiodarone, an inhibitor of CYP3A4, 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

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

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 amiodarone.

Other substances metabolised by cytochrome P450 3A4
Examples of such drugs are lidocaine, 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.

Effect 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 amiodarone.

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

Other medicinal product interactions with amiodarone (see *Warnings and Precautions*)
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 for this bradycardia effect is unknown. If co-administration cannot be avoided, cardiac monitoring is recommended.

PREGNANCY AND LACTATION

Pregnancy
Amiohexal 200 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 10-25% 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.
Amiohexal 200 must not be used during pregnancy unless clearly necessary. Due to the long half-life of amiodarone, women who want to become pregnant 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
Transition into mother's milk is proven for the active substance and the active metabolite. Measurable plasma levels are reached in breast- fed children. If treatment is necessary in the lactation period or if **Amiohexal 200** has been taken during pregnancy, breast-feeding should be refrained from.

SIDE EFFECTS

Blood and lymphatic system disorders
Very rare: Thrombocytopenia, haemolytic or aplastic anaemia
Not known: Neutropenia, agranulocytosis

Immune system disorders
Not known: Angioedema (Quincke's oedema), anaphylactic reactions including anaphylactic shock

Endocrine disorders
Common: Hyperthyroidism or hypothyroidism. Severe hyperthyroidism, in some cases with fatal outcome, has been described.
Very rare: Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Metabolic and nutrition disorders
Not known: Decreased appetite

Psychiatric disorders
Uncommon: Decreased libido
Not known: Delirium (including confusion), hallucinations

Nervous system disorders
Common: Extrapyramidal tremors, nightmares, dyssomnia, sensory, motor or mixed peripheral neuropathy
Uncommon: Peripheral sensory neuropathy and/or myopathy, usually reversible after discontinuation of treatment, dizziness
Very rare: Benign increases of intracranial pressure (pseudotumor cerebri), cerebral ataxia, headaches
Not known: Parkinsonism, parosmia

Eye disorders
Very common: Microdeposits at the anterior surface of the cornea (can also be described as Cornea verticillata) usually limited to the area under the pupil and may cause impaired vision (blurred vision, coloured halos around light sources). The microdeposits consist of complex lipid deposits and are usually reversible within 6 - 12 months after discontinuation.
Very rare: Optic neuropathy and/or optic neuritis that may progress to blindness

Cardiac disorders
Common: Bradycardia (usually moderate and dose- dependent)
Uncommon: Conduction disturbances (SA block, AV block); in individual cases asystole was observed.
Proarrhythmic effects such as changes or enhancement of the cardiac arrhythmia, which may cause a severe impairment of cardiac activity with the possible consequence of cardiac arrest.
Very rare: Marked bradycardia or sinus node arrest especially in elderly patients or with impaired sinus node function.
Not known: Torsades des pointes
Individual cases of ventricular fibrillation / flutter have been described.

Vascular disorders
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders
Common: As a result of the pulmonary toxicity of amiodarone, atypical pneumonia as symptom of a hypersensitivity reaction (hypersensitivity pneumonitis), alveolar or interstitial pneumonitis or fibroses, pleuritis, bronchiolitis obliterans with pneumonia/BOOP may occur. Individual cases with fatal outcome, have been reported.
Non-productive cough and dyspnoea are often first signs of the pulmonary alterations mentioned above. Furthermore, weight loss, fever, asthenia may occur.

Very rare: Bronchospasm in patients with severe respiratory failure and especially in patients with asthma.
Cases of shock lung (ARDS) occurred mostly after surgery, in individual cases with fatal outcome (possible interaction with high oxygen concentration).
Not known: Pulmonary haemorrhage

Gastrointestinal disorders
Very common: Nausea, vomiting, taste disturbances at the beginning of treatment (during ingestion of the loading dose), which disappear with dose reduction.
Common: Constipation
Uncommon: Dry mouth
Not known: Pancreatitis (acute)

Hepatobiliary disorders
Very common: Isolated elevation of serum transaminases at the beginning of therapy, which are generally moderate (1.5- to 3-fold the normal value). The values usually normalize spontaneously or with dose reduction.
Common: Acute hepatitis with high serum transaminases and/or cholestatic icterus, including hepatic failure, in some cases fatal.
Very rare: Chronic liver disease (in some cases with fatal outcome), liver cirrhosis

Skin and subcutaneous tissue disorders
Very common: Photosensitisation with increased tendency to sunburns, which can lead to erythema and rash.
Common: Eczema. During longer-term treatment, especially body areas exposed to sunlight may become hyperpigmented with black-violet to slate-grey discolouration of the skin (pseudocyanosis). The discolouration slowly recedes within 1-4 years after discontinuing the preparation.
Very rare: Erythema during the course of radiation therapy, erythema nodosum and little specific exanthema, exfoliative dermatitis, alopecia.
Not known: 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
Common: Muscle weakness.
Not known: Lupus-like syndrome

Renal and urinary disorders
Rare: Impaired renal function (temporarily)

Reproductive system and breast disorders
Very rare: Epididymitis, impotence

General disorders and administration site disorders
Uncommon: Fatigue
Not known: Granuloma, including bone marrow granuloma

Investigations
Very rare: Increased serum creatinine

Injury, poisoning and procedural complications
not known: Potentially fatal primary graft dysfunction post cardiac transplant (See *Warnings and Precautions*)

SYMPTOMS AND TREATMENT OF OVERDOSE

Little is known to date about acute overdose with **Amiohexal 200.** On account of specific pharmacokinetics, overdose is possible in general only in the course of long-term therapy. The symptoms are usually confined to sinus bradycardia, sino-auricular and nodal disturbances in stimulus conduction as well as tachycardia interrupting spontaneously. Cases of *torsades de pointes*, cardiovascular failure and liver failure have been reported. Amiodarone-induced bradycardia is atropine-resistant. Temporary pacemaker monitoring may therefore possibly be necessary.

Treatment: Management of amiodarone overdosage generally involves symptomatic and supportive care, with ECG and blood pressure monitoring. For bradycardia, IV administration of a beta- adrenergic agonist (e.g. isoproterenol) or use of a transvenous cardiac pacemaker is recommended; amiodarone-induced bradycardia generally is not fully responsive to atropine.
For AV block, the use of a transvenous cardiac pacemaker may be necessary. Administration of IV fluids and placement of the patients in Trendelenburg's position is recommended for the initial treatment of hypotension. An inotropic agent or vasopressor (e.g., dopamine, norepinephrine) should be given for hypotension accompanied by signs of inadequate tissue perfusion. Neither amiodarone nor its metabolites is dialyzable.

ACTIONS

The antiarrhythmic effect of **Amiohexal 200** may be due to at least two major properties:
(i) a prolongation of the myocardial cell-action potential duration and refractory period and
(ii) non-competitive alpha and beta- adrenergic inhibition.

Amiohexal 200 prolongs the duration of the action potential of all cardiac fibers while causing minimal reduction of dV/dt (maximal upstroke velocity of the action potential). The refractory period is prolonged in all cardiac tissues. **Amiohexal 200** increases the cardiac refractor period without influencing resting membrane potential, except in automatic cells where the slope of the prepotential is reduced, generally reducing automaticity. These electrophysiologic effects are reflected in a decreased sinus rate of 15 to 20%, increased PR and QT intervals of about 10% the development of U-wave, and changes of T-wave contour. These changes should not require discontinuation of Amiohexal 200, as they are evidence of its pharmacological action, although Amiohexal 200 can cause marked sinus bradycardia or sinus arrest and heart block. On rare occasions, QT prolongation has been associated with worsening of arrhythmia.

PHARMACODYNAMICS

There is no well-established relationship of plasma concentration to effectiveness, but it does appear that concentrations much below 1 mg/L are often ineffective and that levels above 2.5 mg/L are generally not needed. Within individuals dose reductions and ensuing decreased plasma concentrations can result in loss of arrhythmia control. Plasma-concentration measurements can be used to identify patients whose levels are unusually low, and who might benefit from a dose increase, or unusually high, and who might have dosage reduction in the hope of minimizing side effects. Some observations have suggested a plasma concentration, dose, or dose/duration relationship for side effects such as pulmonary fibrosis, liver-enzyme elevations, corneal deposits and facial pigmentation, peripheral neuropathy, gastrointestinal and central nervous system effects.

PHARMACOKINETICS

Following oral administration in man, amiodarone is slowly and variably absorbed. Oral bioavailability has varied between 30 and 80% along with individual patients (mean value around 50%). Maximum plasma concentrations are attained 3 to 7 hours after a single dose. Despite this, the onset of action may occur in 2 to 3 days, but more commonly takes 1

to 3 weeks, even with loading doses. Plasma concentrations with chronic dosing at 100 to 600 mg/day are approximately dose proportional, with a mean 0.5 mg/L increase for each 100 mg/day. These means, however, include considerable individual variability.
Amiodarone is highly protein-bound (approximately 96%). It has a very large but variable volume of distribution, averaging about 60 L/kg, because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of amiodarone, desethylamiodarone; it accumulates to an even greater extent in almost all tissues. During chronic treatment, the plasma ratio of metabolite to parent compound is approximately one.

The main route of elimination is via hepatic excretion into bile, and some enterohepatic recirculation may occur. However, its kinetics in patients with hepatic insufficiency have not been elucidated. Amiodarone has a very low plasma clearance with negligible renal excretion, so that it does not appear necessary to modify the dose in patients with renal failure.
In patients, following discontinuation of chronic oral therapy, amiodarone has been shown to have a biphasic elimination with an initial one-half reduction of plasma levels after 2.5 to 10 days. A much slower terminal plasma-elimination phase shows a half-life of the parent compound ranging from 26 to 107 days, with a mean of approximately 53 days and most patients in the 40 to 55-day range. In the absence of a loading-dose period, steady state plasma concentrations, at constant oral dosing, would therefore be reached between 130 and 535 days, with an average of 265 days. For the metabolite, the mean plasma-elimination half-life was approximately 61 days. These data probably reflect an initial elimination of drug from well-perfused tissue (the 2.5- to 10-day half-life phase), followed by a terminal phase representing extremely slow elimination from poorly perfused tissue compartments such as fat.
Amiodarone and its metabolite have a limited transplacenta transfer of approximately 10 to 50%. The parent drug and its metabolite have been detected in breast milk.

PACKING / PACK SIZES
Blister pack of 20, 50 & 100 tablets in a box.

STORAGE CONDITION
Do not store above 30 °C.
Protect from heat, moisture and direct light. Keep out of the reach of children.
(Jauhi daripada kanak-kanak)

Shelf life: Please refer to the outer box label.

Manufactured by:
Salutas Pharma GmbH
Otto-von-Guericke-Allee 1,
D-39179 Barleben, Germany.

For:

HEXAL AG
Industriestraße 25,
D-83607 Holzkirchen, Germany.

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This product is to be used only by a registered medical practitioner with experience in cardiology.