UNILAB

Amiodarone HCl

Rythma®
200 mg Tablet
Antiarrhythmic agent

Rx

FORMULATION

Each tablet contains 200 mg amiodarone hydrochloride.

PHARMACEUTICAL FORM

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

CLINICAL PARTICULARS

Therapeutic indications

Symptomatic and tachycardiac supraventricular arrhythmias requiring treatment such as

- A-V-junctional tachycardia
- supraventricular tachycardia associated with Wolff-Parkinson-White syndrome or
- paroxysmal atrial fibrillation

This indication applies to patients who do not respond to other antiarrhythmics or for whom other antiarrhythmics are not indicated.

- Severe symptomatic tachycardiac ventricular arrhythmias

It should be noted that a therapy with beta-blockers should not be stopped in favor for a treatment with amiodarone.

Dosage and method of administration

In patients with ventricular arrhythmias, adjustment to the antiarrhythmic requires careful cardiologic monitoring and may only be carried out if cardiologic emergency equipment is available and monitoring control possible.

Dosage with single and daily dose
As saturation dose 600 mg amiodarone per day (200 mg amiodarone 3 times per day) for 8-10 days.
In some cases, doses of up to 1,200 mg amiodarone per day (200 mg amiodarone 6 times per day) may become necessary.

Afterwards, reduction to a maintenance dose, usually 200 mg Amiodarone per day for 5 days per week.
In some cases, higher doses of 200-600 mg amiodarone per day (1-3 times 200 mg amiodarone) are required during long-term therapy.

Special note
As most of adverse reactions are dose-dependent, the lowest effective maintenance dose should be administered.

Paediatric population
The safety and efficacy of amiodarone in children has not been established.
Currently available data are described in Pharmacodynamic and Pharmacokinetic properties.

In children, the dose should be adjusted according to the body surface or body weight.

Method and duration of administration

The tablets should be taken unchewed during or after meals together with sufficient liquid.

The attending physician decides on the duration of administration.

Contraindications

Amiodarone must not be used in:

- hypersensitivity to amiodarone or to any of the other excipients
- sinus bradycardia (less than 55 pulse beats per minute)
- all forms of delayed conduction (sinoauricular and nodal conduction delay) including sick sinus syndrome, AV-blocks of second and third degrees as well as bifascicular and trifascicular blocks if no pacemaker is used.
- thyropathy
- pre-existing QT prolongation
- hypokalaemia
- allergy to iodine
- concomitant treatment with MAO inhibitors
- concomitant treatment with medicinal products which may induce *Torsades de Pointes* (see also Interaction with other medicinal products and other forms of interaction).
- pregnancy, unless clearly indicated (see Pregnancy and lactation)
- lactation (see Pregnancy and lactation)

Special warnings and precautions for use

Warnings

Cardiovascular system (see Undesirable 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 amiodarone.
There is an increased risk of *Torsades de Pointes* in case of an excessive QT prolongation.

As a consequence of the pharmacological action of amiodarone 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 amiodarone mainly occur in connection with QT-prolonging factors, such as medicinal product interactions and/or electrolyte imbalance (see Interaction with other medicinal products and other forms of interaction and Undesirable effects). Despite QT prolongation amiodarone shows a low torsadogenic activity.

Severe bradycardia (see Interaction with other medicinal products and other forms of interaction)
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 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.

Hyperthyroidism (see Precautions and Undesirable effects)
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.

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 medicinal products, beta-blockers, and/or corticosteroids has to be started.

Lung (see Undesirable effects)
There is the risk of developing severe inflammatory pneumopathy (hypersensitivity pneumonitis, alveolar or interstitial pneumonitis) during therapy with amiodarone.
Non-productive cough and dyspnoea are common symptoms of the above mentioned pulmonary changes. Furthermore, weight loss, fever, weakness may occur.

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.

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, amiodarone 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. If amiodarone is withdrawn early, interstitial pneumonia usually recedes.

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 Interaction with other medicinal products and other forms of interaction).

Liver (see Undesirable 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 dose form of amiodarone (with intravenous application already during the first 24 hours). Therefore, the dose should be reduced or amiodarone discontinued if transaminase levels increase to values exceeding 3 times the norm.

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 amiodarone, but cases with fatal outcome have been reported.

Severe bullous skin reactions (see Undesirable 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), amiodarone must be discontinued immediately.

Neuromuscular disorders (see Undesirable effects)
Amiodarone can cause peripheral neuropathy and/or myopathy. These usually disappear a few months after discontinuation of amiodarone therapy, but may not be completely reversible in some cases.

Eyes (see Undesirable 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 Interaction with other medicinal products and other forms of interaction)
The concomitant use of amiodarone 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 3A4. Therefore statins that are metabolized by CYP3A4 (e.g. simvastatin, atorvastatin, lovastatin) should not be used concomitantly with amiodarone.

Precautions
For preliminary examinations and monitoring of the patients see also Warnings and Undesirable effects.

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.

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.

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 reevaluated, 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.

For prognosis and progression of the lung see Warnings and Undesirable effects.

Endocrine disorders (see Warnings and Undesirable effects)
Due to the risk of developing a thyroid dysfunction (hyperthyroidism or hypothyroidism) on treatment with amiodarone, 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.

Amiodarone 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 amiodarone.

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, normalisation of the thyroid function occurs usually within 1-3 months.

The amiodarone dose should - if possible - be reduced and / or substitution with levothyroxine be started if hypothyroidism is detected. In individual cases, a discontinuation of amiodarone may be required.

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

Skin
Exposure to sunlight should be avoided during therapy with amiodarone; 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 amiodarone, a light protector is necessary for some more time.

Anaesthesia (see Interaction with other medicinal products and other forms of interaction and Undesirable effects)
Prior to surgery, the anaesthesiologist should be informed about the amiodarone therapy.

Paediatric population (see Dosage and method of administration, Pharmacodynamic properties and Pharmacokinetic properties)
The safety and efficacy of amiodarone in children has not been established. Therefore, administration in children is not recommended.

Interaction with other medicinal products and other forms of interaction
Pharmacodynamic interactions
Medicinal products inducing *Torsades de Pointes* or prolonging QT

Medicinal products inducing Torsades de Pointes
Combined therapy with the following medicinal products which prolong the QT interval is contra-indicated (see Contraindications) due to the increased risk of *Torsades de Pointes*; for example:

- Class IA anti-arrhythmic substance e.g. quinidine, procainamide, disopyramide
- Class III anti-arrhythmic medicinal products 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

Medicinal products prolonging QT interval
Co-administration of amiodarone with medicinal products 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 *Torsades de Pointes* may increase and patients should be monitored for QT prolongation.

Concomitant use of amiodarone with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contra-indicated).
There have been rare reports of QTc interval prolongation, with or without T*orsades de Pointes*, in patients taking amiodarone with fluoroquinolones (see Contraindications).

Medicinal products lowering heart rate or causing automaticity or conduction disorders
Combined therapy with the following substances 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.

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 medicinal products 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 anaesthesia
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
The dose of warfarin 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), and plasma levels may be measured.

CYP P450 3A4 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 is increased by concomitant administration of amiodarone with statins metabolized by CYP3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolized by CYP3A4 when given with amiodarone.

Other substances metabolized by cytochrome P450 3A4
Examples of such medicinal products are lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine ergotamine and colchicine.

CYP2D6 substrates
Flecainide
Given that flecainide is mainly metabolized 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 Special warnings and precautions for use)
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 (see Special warnings and precautions for use).

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 10-25% 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.

Amiodarone must not be used during pregnancy unless clearly necessary.
Due to the long half-life of amiodarone, 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.

Breast-feeding
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 amiodarone has been taken during pregnancy, breast-feeding should be refrained from.

Effects on ability to drive and use machines
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.

Undesirable effects
The evaluation of undesirable effects is based on the following information on frequency:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Not known	(cannot be estimated from the available data)

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

Immune system disorders
Not known: Angioedema (Quincke's edema), anaphylactic reaction, anaphylactic shock

Endocrine disorders
Common: Hyperthyroidism or hypothyroidism. Severe hyperthyroidism, in some cases with fatal outcome, has been described.

(For follow-up examinations, diagnostic and therapeutic measures, see Special warnings and precautions for use.)

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
Uncommon: Peripheral sensory neuropathy and/or myopathy, usually reversible after discontinuation of treatment (see Special warnings and precautions for use), dizziness
Very rare: Benign increases of intracranial pressure (pseudotumour 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 (see Special warnings and precautions for use).

Cardiac disorders
Common: Bradycardia (usually moderate and dose-dependent).
Uncommon: Conduction disturbances (SA block, AV block); in individual cases asystole was observed (see Special warnings and precautions for use).
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 (see Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction).

Very rare: Marked bradycardia or sinus node arrest especially in elderly patients or with impaired sinus node function (see Special warnings and precautions for use).
Not known: *Torsades de Pointes* (see Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction)

Individual cases of ventricular fibrillation flutter have been described (see Special warnings and precautions for use concerning follow-up examinations, diagnostic and therapeutic measures).

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 (see Special warnings and precautions for use). 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, see Interaction with other medicinal products and other forms of interaction).

Not known: Pulmonary haemorrhage

(For follow-up examinations, diagnostic and therapeutic measures, see Special warnings and precautions for use.)

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 normalise 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

(For follow-up examinations, diagnostic and therapeutic measures, see Special warnings and precautions for use.)

Skin and subcutaneous tissue disorders
Very common: Photosensitisation with increased tendency to sunburns, which can lead to erythema and rash (see Special warnings and precautions for use)
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, as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), bullous dermatitis, Drug reaction with eosinophilia and systematic symptoms (DRESS).

(For preventive measures, see Special warnings and precautions for use).

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

Overdose
Little is known to date about acute overdose with amiodarone. 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, sinoauricular 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 is symptomatic. In case of suspected overdose, the patient should be observed for a sufficiently long time in special view of the cardiac situation due to the pharmacokinetics of amiodarone.

Neither amiodarone nor its metabolites are dialyzable.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, anti-arrhythmics, class I and III, anti-arrhythmics, class III
ATC code: C01BD01

In myocardial tissue, amiodarone inhibits the potassium efflux during stage III of the action potential and thus selectively prolongs the duration of repolarization and the refractory period of the action potential (class III effect as defined by Vaughan Williams). This leads to depression of ectopias and re-entry mechanisms without impaired contractile force of the myocardium.

Amiodarone reduces conduction velocity and extends the refractory time in accessory atrioventricular paths.

The prolongation of the slow diastolic depolarization in the pacemaker potential leads to a depressed automatism in the pacemaker tissue with deceleration of the heart rate which is atropine-resistant.

Amiodarone exhibits a dose-dependent, non-competitive inhibition of alpha- and beta-adrenergic activities, which is hemodynamically expressed by a coronary-dilative and vasodilative effect and also by improvement in the oxygen balance.

Amiodarone administered orally does not show any significantly negative inotropic effect.

In case of i.v. administration, reduced contractility may occur particularly after injection.

Paediatric population
No controlled paediatric studies have been undertaken.

In published studies, the safety of amiodarone was evaluated in 1,118 paediatric patients with various arrhythmias. The following doses were used in paediatric clinical trials.

Oral
- Loading dose: 10 to 20 mg/kg/day for 7 to 10 days (or 500 mg/m^2/day if expressed per square meter)
- Maintenance dose: the minimum effective dose should be used; according to individual response, it may range between 5 to 10 mg/kg/day (or 250 mg/m^2/day if expressed per square meter)

Pharmacokinetic properties

Amiodarone is metabolized mainly by CYP3A4, and also by CYP2C8. Amiodarone and its metabolite, desethylamiodarone, exhibit a potential *in vitro* to inhibit CYP1A1, CYP1A2, CYP2C9, CYP2D6, CYP3A4, CYP2A6, CYP2B6 and CYP2C8. Amiodarone and desethylamiodarone have also a potential to inhibit some transporters such as P-gp and organic cation transporter (OCT_2) (one study shows a 1.1% increase in concentration of creatinine (an OCT_2 substrate). In vivo data describe amiodarone interactions on CYP3A4, CYP2C9, CYP2D6 and P-gp substrates.

After oral administration, approximately 50% of amiodarone is absorbed in the gastrointestinal tract.

After administration of one single dose, plasma levels are reached after 3-7 hours.

Accumulation of the substance at its site of action or saturation of the myocardial tissue, respectively, is decisive for therapeutic efficacy.

Depending on the saturation dose, the onset of action can be expected within a period of a few days up to two weeks.

Following injection, the maximum action is achieved after 15 minutes.
Afterwards, re-distribution into tissue and rapid decrease in the plasma concentrations occur within 4 hours.

For saturation of tissue depots, therapy must be continued intravenously or orally.

Amiodarone has a long half-life interindividually, varying between 20 and 100 days.

During saturation, the substance accumulates mainly in fat tissue. Steady state is attained within a period of one month up to several months.

Due to these characteristics, the recommended saturation dose should be administered in order to attain rapid saturation in tissue which is required for therapeutic efficacy.

The main excretion route is through liver and bile; 10% of the substance is excreted renally.

Due to low renal excretion, the usual dose can be administered to patients suffering from renal insufficiency.

After withdrawal, amiodarone is still excreted for several months.

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

Preclinical safety data

Acute toxicity

Acute toxicity of amiodarone seems to be relatively low, and LD_{50} values are more than 3 g/kg BW. Clinical symptoms were vomiting in the dogs, CNS effects (sedation, tremor, convulsions, dyspnea) in rodents.

Chronic toxicity/subchronic toxicity

Chronic toxicity studies revealed that amiodarone has a similar toxicological potential in animals as well as in humans. Amiodarone caused pulmonary damage such as fibrosis or phospholipidosis (in hamster, rat and dog) as well as CNS disturbances (in rats). Oxidative stress and free radicals seem to be very important for inducing pulmonary damage. Furthermore, amiodarone caused hepatic damage in rats. Effects of amiodarone on serum lipids may be indirectly caused by alterations in the plasma concentrations of thyroid hormones.

Mutagenic and tumorigenic potential

Amiodarone is a highly phototoxic substance. There is evidence that free cytotoxic radicals are formed via UV irradiation in the presence of amiodarone. This may not only lead to acute phototoxic reactions, but also to damage of DNA (photomutagenicity) and subsequently to photocancerogenic effects. These potentially severe adverse reactions of amiodarone have not been investigated in experiments up to now. Therefore, the photomutagenic and photocancerogenic potential of amiodarone is not known.

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.

Reproductive toxicity

Increased serum levels for LH and FSH pointing to testicular dysfunction were measured in male patients after longer-term treatment.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable

Storage

Store at temperatures not exceeding 25°C.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-**UNILAB**-1 (+632-8- **864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph.

By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY

Alu/ White Opaque PP Blister Pack of 10's (Box of 30's)

REGISTRATION NUMBER AND DATE OF FIRST AUTHORIZATION

DRP-1193-01, 07-2010

DATE OF REVISION

September 2019
CDSv04

Reg. IPOPHIL

Manufactured by **Salutas Pharma GmbH**
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