PATIENT INFORMATION LEAFLET

CORDALİN 150 mg / 3 mL I.V. Injectable Solution
Administered intravenously

- ***Active ingredient:*** 150 mg Amiodarone hydrochloride
- ***Excipients:*** Benzyl alcohol, Tween 80 and water for injection.

Before using this medicine, read all of this PATIENT INFORMATION LEAFLET carefully. Because, this leaflet includes important information for you.

- *Keep this PATIENT INFORMATION LEAFLET. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you. Do not pass it on to others.*
- *During the use of this medicine, tell that you are using this medicine when you go to a doctor or hospital.*
- *Follow these instructions exactly as written. Do not use **higher or lower** dose other than your recommended dose.*

In this patient information leaflet:

Headings are included.

1. What CORDALİN is and what it is used for?

CORDALİN contains 150 mg amiodarone hydrochloride active substance in 3 mL ampoules.
CORDALİN is available in packages containing 6 ampoules.
CORDALİN is a drug called antiarrhythmic and used in the treatment of heart rhythm disorders. It is used in the treatment of conditions such as excessively rapid heartbeat and irregular heart rhythm.
Your doctor may have prescribed CORDALİN administered intravenously to you, in cases where it is not possible to administer tablets containing amiodarone orally and for one or more of the following reasons;

- Conditions with excessive heart beat or rhythm disturbance in the heart
- Acceleration of heartbeat due to a pronounced rhythm and conduction disorder called Wolf-Parkinson White syndrome
- To maintain a normal rhythm in case of irregularity in your heart beat.

2. Before you are given CORDALİN

DO NOT USE CORDALİN in the following cases:

If;

- You have a heart block condition that manifests itself as heartbeats that are too fast or too slow or irregular.
- You have a message disorder
- You have a disease related to the thyroid gland
- You are allergic to the active substance amiodarone or other substances contained in the drug
- You are allergic to iodine
- You are pregnant or breastfeeding your baby
- With drugs that cause torsades de pointes (serious heart rhythm disorder):
  -Class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide)
  -Class III antiarrhythmics (dofetilide, ibutilide, sotalol)
  - Other drugs: Bepridil, cisapride, diphemanil, IV erythromycin, mizolastine, IV vincamine
  - When used with sulpiride, there is an increased risk of serious heart rhythm disturbances.
- Severe low blood pressure condition
- Severe respiratory failure
- In cases of heart muscle disease or heart failure
- Children under 3 years of age due to the benzyl alcohol content
- Non-cardiac rhythm medications; some neuroleptic agents, pentamidine (when administered intravenously)
- Use with Sparfloxacin.

Take SPECIAL CARE with CORDALİN in the following cases:

If;

- You have low blood pressure
- You have liver disease
- You have any lung disease, including asthma
- You are using tablets containing amiodarone
- You are of advanced age (may significantly reduce the heart rate).
- You have heart failure
- Long QT syndrome (a condition in the heart that can lead to serious arrhythmias and sudden death) or Torsades de Pointes (life-threatening irregular heart rhythm) disease
- You have a dysfunction related to the thyroid gland (your doctor will keep this situation under control by performing blood tests before, during and after treatment.)
- In case of breathing difficulty or dry cough alone or with poor general condition.
- A condition with electrolyte disturbance (especially if you have a condition such as potassium deficiency, this should be corrected before taking this drug.)
- Exposure to direct sunlight (signs of sensitivity such as skin rash, rash and discoloration may appear). You should use a sunscreen.

- You are going to undergo surgery and you will be anesthetized

These warnings are valid for you, even at any time in the past, please consult your doctor.
Treatment with CORDALİN requires continuous medical supervision. Before starting treatment and during your treatment, your doctor may want to monitor your medical condition by performing triggers such as blood tests, chest X-ray and eye examination, and ECG.

Use of CORDALİN with food and drink
CORDALİN is used by intravenous or intramuscular injection (as an infusion). Therefore, it is not expected to interact with food and drink.
When using CORDALİN, be careful not to consume grapefruit juice.

Pregnancy
Consult your doctor or pharmacist before using the medicine.
You should not use CORDALİN during your pregnancy.
If you notice that you are pregnant during your treatment, consult your doctor or pharmacist immediately.

Breast-feeding
Consult your doctor or pharmacist before using the medicine.
The drug passes into breast milk and may cause unwanted effects on the thyroid in the baby, so you should not use CORDALİN during breastfeeding.

Driving and using machines
No interactions have been reported.

Important information about some of the excipients contained in CORDALİN content
CORDALİN contains benzyl alcohol. It should not be administered to premature babies and newborns. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.

Using other medicines
Since CORDALİN remains in the body for a long time even after treatment is discontinued, drug interactions may occur even months after treatment is discontinued.
<u>CORDALİN should not be used together with the following drugs:</u>

- Medicines that cause life-threatening irregular heart rhythm (torsades de pointes): For example;

  - Quinidine, hydroquinidine, disopyramide (used to treat irregular heartbeat)

  - Sotalol, dofetilide, ibutilide (used in the treatment of irregular heart beat), intravenous erythromycin, mizolastine, sparfloxacin, sultopride, co-trimoxazole and pentamidine (antibiotics used in the treatment of infection),

  - Bepridil (used in the treatment of chest pain due to impaired heart muscle blood flow), cisprid (used in the treatment of indigestion), intravenous vincamine (used to treat symptomatic disorders related to mental functions in the elderly),

  - Drugs used in the treatment of malaria such as quinine, mefloquine, chloroquine,

halofantrine,

- Medicines used in the treatment of allergies such as terfenadine, astemizole, mizolastine,
- Medicines used in some mental disorders such as chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride, sertindole
- Lithium (used in the treatment of mental illness called bipolar disorder),
- Tricyclic antidepressants used in the treatment of depression such as doxepin, maprotiline, amitriptyline,
- Moxifloxacin (an antibiotic used to treat infections)
- Stimulating constipation medications.

CORDALİN is not recommended to be used with the following drugs:

- Some drugs used for the treatment of mental illnesses (e.g.; thioridazine, levomepromazine, trifluoperazine, cyanamazine, sulpiride, tiapride, pimozide, droperidol)
- Diltiazem used intravenously (used in the treatment of chest pain and high blood pressure due to impaired heart muscle blood flow),
- Some drugs used in the treatment of heart diseases and blood pressure called beta blockers (except sotalol and esmolol)
- Fluoroquinolones (a group of antibiotics used to treat infections).

Caution should be exercised when CORDALİN is used with the following drugs:

- Medicines used to thin the blood (effects of such drugs that prevent clotting may increase, bleeding risk may occur).
- Statins used to lower blood fat levels such as simvastatin, atorvastatin and lovastatin (concomitant use increases the risk of muscle toxicity).
- Fentanyl, a potent pain reliever used during surgery (concomitant use increases the risk of toxicity).
- Lidocaine (used in anesthesia), tacrolimus (used to prevent organ rejection after organ transplantation), sildenafil (used to treat impotence), midazolam and triazolam (used as preoperative sedatives), dihydroergotamine and ergotamine (used to treat migraine), colchicine (used to treat gout) used to treat disease); it can cause the blood levels of these drugs to increase and their toxicity to increase.
- Flecainide used to treat cardiac arrhythmias (the dose of this drug may need to be reduced by half).
- Cyclosporine used to prevent organ rejection after transplantation (risk of harmful effects on kidneys).
- Diltiazem taken orally and used in the treatment of chest pain and high blood pressure that develops due to impaired heart muscle blood flow (especially in the elderly, there may be a risk of heart block, excessive slowing of the heart rate).
- Digoxin used to treat heart failure (risk of heart block, excessive slowing of the heart rate).
- Esmolol used to treat heart beat disorder (heart rhythm disturbances may occur).
- Potassium-lowering drugs: Potassium-lowering diuretics (used alone or in combination), stimulant laxatives, glucocorticoids (systemic use), tetracosactide, amphotericin B (heart

rhythm disturbances may occur).

- Phenytoin used in the treatment of epilepsy (if used together, the level of this drug in the blood may increase)
- Medications that reduce heart rate [eg; calcium antagonists (diltiazem, verapamil); beta blockers (excluding sotalol); clonidine, guanfacine, cardiac glycosides, mefloquine, anticholinesterase drugs (donezepil, galantamine, rivastigmine, tacrine, ambemony, pyridostigmine, neostigmine) rhythm disturbances may occur].
- Drugs used in anesthesia (slowing in heart rate, low blood pressure, heart disorders, respiratory disorders can be seen immediately after surgery).

If you are currently using or have recently used any prescribed or non-prescribed medicine, please inform your doctor or pharmacist.

3. How to use CORDALİN

Instructions for use and dose/frequency of administration:

CORDALİN is used only in the hospital, under the supervision of a doctor and by checking blood pressure and ECG.

CORDALİN will be diluted before it is administered to you.

Your doctor will start treatment with a tablet containing amiodarone as soon as it is appropriate.

Your doctor will determine the dose to be administered for you, taking into account your situation.

Usually the treatment is conducted as follows:

Loading therapy: The average dose is 5 mg per kilogram (eg 450 mg or 3 ampoules in a 90 kilogram person). This dose is administered over a period of 20 minutes to 2 hours and is repeated 2 or 3 times in 24 hours.

Maintenance treatment: Depending on the condition of your illness, you can be administered at a dose of approximately 15 mg per kilo per day (average 600-800 mg or 4-5 ampoules in 24 hours). Maximum 1200 mg (8 ampoules) can be given in 24 hours.

In emergencies: Your doctor may give you a dose of 150 mg-300 mg by slow injection for 3 minutes.

Your doctor will tell you how long your treatment will take with CORDALİN.

Your doctor will determine the dose of your medicine depending on your illness and administer it to you.

Route of administration and method:

CORDALİN injectable solution should be administered into a central vein in the head and neck region (central venous route).

It should be given by slow drop infusion (preferably using an infusion pump) using only isotonic glucose (dextrose) solution.

Due to the formulation of the product, the drug should not be used at a concentration of less than 2 ampoules in 500 ml. Only isotonic glucose (dextrose) solution should be used. No other product should be added to the infusion solution.

Different age groups:

Use in children:

Its efficacy and safety in children have not been proven. Because it contains benzyl alcohol, it should not be used in children under 3 years of age.

Use in the elderly:
The dosage used in the elderly is generally the same as in adults. The doctor may prescribe a lower dose of CORDALİN and may want to monitor your heart rate and thyroid functions closely.

Conditions of special use:
CORDALİN should only be used in a hospital environment and under continuous control (ECG, blood pressure).
To detect liver damage caused by CORDALİN, your doctor may want to monitor your liver functions at regular intervals.
If you have the impression that the effect of CORDALİN is too strong or too weak, talk to your doctor or pharmacist.

If you use more CORDALİN than you should:
CORDALİN is only used in the hospital, under the supervision of a doctor and under constant control (ECG, blood pressure).
If you use more CORDALİN than you should, talk to a doctor or pharmacist.

If you forget to use CORDALİN:
CORDALİN is only used in the hospital, under the supervision of a doctor and under constant control (ECG, blood pressure).
Do not take double doses to make up for forgotten doses.

If CORDALİN treatment ends, effects may occur:
CORDALİN is only used in the hospital, under the supervision of a doctor and under constant control (ECG, blood pressure).

4. Possible side effects

Like all other medicines, CORDALİN may cause side effects in patients with hypersensitivity to any component of the drug.

The frequency of adverse events is reported using the following categories;

Very common : can be seen at least 1 out of 10 patients.
Common : can be seen less than one in 10 patients, but more than one in 100 patients.
Uncommon : can be seen less than one in 100 patients, but more than one in 1,000 patients.
Rare : can be seen less than one in 1.000 patients, but can be seen more than 10,000 patients in one.
Very rare : can be seen less than one in 10,000 patients.
Unknown : cannot be estimated from available data.

If any of the following occur, stop using CORDALİN and IMMEDIATELY inform your doctor or go to the nearest emergency department:
- If you have an allergic reaction; rash, difficulty swallowing or breathing, swelling of the eyelids, face, lips, throat, or tongue
These are all very serious side effects. If you have one of these, it means you have a serious allergy to CORDALİN.
You may need urgent medical attention or hospitalization.

Common:

- Yellowing of the skin or eyes (jaundice), tiredness, nausea, loss of appetite, stomach pain or high fever (these may be signs of liver problems or damage).
- Difficulty breathing, persistent cough, wheezing, weight loss and fever (these may be signs of a potentially dangerous pneumonia).

Uncommon:

- Your heartbeat becomes irregular, unstable (this can lead to a heart attack).
- Numbness, weakness, tingling or burning sensation in any part of your body.

Very rare:

- Vision loss in one eye or blurred and discolored vision. There may be burning and tenderness in your eyes, and pain when you move your eyes. These may be signs of a disease called optic neuropathy or neuritis.
- Your heartbeat slows down so that it almost stops.
- Redness of the skin due to narrowing or blockage of blood vessels (vasculitis)
- Headache (especially severe in the morning or worsening after coughing and straining), nausea, seizures, fainting, vision problems or confusion. These may be signs of a brain disorder (pseudo-tumor cerebri).
- Jerking or staggering or chattering or slow speech in the mouth.
- Dizziness, lightheadedness, fatigue and shortness of breath, These may be signs of slow heart rate (especially if you are over 65) or other problems that disrupt normal heartbeat.
- Bleeding in the lungs has been reported in some patients. If blood comes out in your cough, inform your doctor immediately.

All these are serious side effects. Emergency medical attention may be required.
Other side effects
Very common:

- Blurred vision or the appearance of colored circles in intense light.
- Nausea or vomiting.
- Taste disturbance.
- Changes in the level of liver enzymes at the start of treatment (you can see the results of laboratory tests).
- Sun sensitivity (protect your skin from sunlight).

Common:

- Extreme restlessness or excitement, weight loss, increased sweating, intolerance to heat;

these may be due to the excessive production of thyroid hormone in the body (hyperthyroidism).

- Extreme tiredness, weakness, feeling exhausted, weight gain, cold intolerance, constipation and muscle aches; These may be due to under-production of thyroid hormone in the body (hypothyroidism).
- Tremors when you move your arms or legs, which usually regress after dose reduction or withdrawal.
- Bluish or gray discoloration of the sun-exposed parts of the body, especially on the skin on the face.
- Slight decrease in dose-dependent heart rate.
- Nightmares.
- Sleep problems.

Uncommon:

- Muscle cramps, stiffness or spasms.

Very rare:

- Swelling of the testicles (epididymitis) - skin rash with rash, hair loss or nail structure and shedding (exfoliative dermatitis).
- Fatigue, weakness, dizziness or pale skin; these can be signs of anemia.
- Bleeding or bruising more easily than normal; these may be signs of thrombocytopenia, a blood cell disorder.
- Moodiness, dizziness or weakness, nausea, loss of appetite, irritability; these may be symptoms of a disease called "inappropriate ADH syndrome".
- Headache
- Balance problems, dizziness, which usually regresses after dose reduction or withdrawal
- Erection or ejaculation problems
- Hair loss, baldness
- Skin rash
- Skin redness during radiotherapy.

Unknown:

- Hives
- Granuloma (granular lump) including bone marrow granuloma

These are mild side effects of CORDALİN.

If you experience any side effects that are not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of the side effects:

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to

your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store CORDALİN

Keep CORDALİN in places out of sight and reach of children and within the packaging.

Store at room temperature below 25 ° C, protect from light.

Use in accordance with the expiry date.

Do not use CORDALİN after the expiration date which is stated on the package.

Marketing Authorization Holder and Manufacturing Site:

Osel İlaç Sanayi ve Ticaret A.Ş

Akbaba Mah. Maraş Cad. No:52

34820 Beykoz/ İSTANBUL

This leaflet was approved on 25/12/2014

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CORDALİN 150 mg / 3 mL I.V. Injectable Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

In 3 mL sterile ampoules;

Amiodarone hydrochloride 150 mg

Excipients:

Benzyl alcohol 60 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Injectable solution.

Pale yellow, clear solution.

4. CLINICAL PARTICULARS

4.1. Therapeutical indications

CORDALİN should be used in the treatment of the following severe rhythm disturbances, when oral administration is not possible.

- Atrial arrhythmia with rapid ventricular rhythm
- Tachycardia due to Wolf-Parkinson White syndrome.
- Diagnosed, symptomatic ventricular arrhythmia.

4.2. Posology and method of administration

Posology / frequency and duration of administration:

Intravenous infusion:

Loading therapy:

The average dose is 5 mg / kg in 250 ml of 5% dextrose solution. This dose is administered over a period of 20 minutes to 2 hours, preferably using an electric syringe (infusion pump), and is administered 2 or 3 times in 24 hours.

The short duration of the effect of the medicinal product necessitates continued infusion.

Maintenance therapy:

It is administered as 10-20 mg / kg / day (average 600-800 mg in 24 hours, maximum 1200 mg in 24 hours) in 250 ml of 5% dextrose solution for several days.

Transition to oral therapy:

Oral treatment is started from the first day of infusion (200 mg tablets 3 times a day). This dose can be increased to 4 or even 5 tablets per day. Intravenous administration should then be phased out.

Intravenous injection:
The dose is 5 mg / kg administered in at least 3 minutes. It should not be mixed with any medication in the same syringe.
Only limited to cardiopulmonary resuscitation of shock-resistant ventricular fibrillation, 300 mg (or 5 mg / kg) amiodarone as the first dose is diluted in 20 ml of 5% dextrose solution i.v. It can be administered by bolus injection. If ventricular fibrillation continues, an additional 150 mg (or 2.5 mg / kg) i.v. dose administration can be considered.

Method of Administration:
Due to the formulation of the product, the drug should not be used in concentrations less than 2 ampoules in 500 mL. Only isotonic glucose (dextrose) solution should be used. No other product should be added to the infusion solution.
Amiodarone should be administered via central venous route.

Incompatibility:
The use of PVC materials or medical devices plasticized with DEHP [di (2-ethylhexyl) phthalate] may result in the release of DEHP in the presence of amiodarone solution for injection. In order to minimize the patient's exposure to DEHP, it is recommended that the final dilution of amiodarone be prepared using DEHP-free hardware, DEHP-free PVC, polyolefins (polyethylene, polypropylene), glass, etc. prior to infusion.

Additional information on special populations:
Hepatic impairment:
Acute liver disorders (severe hepatocellular failure or liver failure, sometimes fatal) or chronic liver disorders may occur within the first 24 hours of intravenous administration of amiodarone. Therefore, if the level of transaminases exceeds three times the normal range, the amiodarone dose should be reduced or treatment discontinued.

Renal impairment:
No special dose adjustment is required for patients with renal insufficiency.

Pediatric population:
The safety and efficacy of Amiodarone in pediatric patients has not been proven. Therefore, it is not recommended for use in pediatric patients. Since it contains benzyl alcohol, it is contraindicated in newborns, infants and children up to 3 years of age.

Geriatric population:
Since CORDALİN is indicated for some diseases, especially in the elderly, the dose in elderly

patients is the same as the dose administered in adults.
As with all patients, it is important to use the minimum effective dose. Although there is no evidence that the dose requirement is different in this age group, elderly patients may become closer to bradycardia and conduction disorders if a very high dose is administered. Special attention should be paid to the monitoring of thyroid function (see sections 4.3, 4.4 and 4.8).

4.3. Contraindications

CORDALİN is contraindicated in the following situations:

- Cases of sinoatrial block or sinus bradycardia without a pacemaker;
- Sick sinus syndrome without a pacemaker (risk of sinus arrest);
- Severe ventricular conduction disturbances without pacemakers;
- In thyroid diseases;
- Hypersensitivity to iodine, amiodarone or any of the excipients;
- During pregnancy (except in exceptional circumstances);
- Lactation (See Section 4.6 "Lactation period");
- II. or III. degree heart block;
- If a pacemaker is not used, bi- or tri-fascicular conduction disturbances, or if the patient is not in the private care unit, amiodarone should be used under electrostatic rate control;
- Bradycardia-induced syncope;
- Circulatory collapse;
- Severe arterial hypotension;
- Use of intravenous injections in cases of hypotension, severe respiratory failure, myocardiopathy or heart failure (worsening of the condition is possible);
- Children under 3 years of age, as it contains benzyl alcohol;
- It is contraindicated to use in combination with the following drugs that cause Torsade de Pointes (See Section 4.5):
  - Class Ia antiarrhythmic agents (quinidine, hydroquinidine, disopyramide)
  - Class III antiarrhythmic agents (sotalol, bepridil, dofetilide, ibutilide)
  - Other drugs such as mizolastine, diphemanil, vincamine, some neuroleptic agents, cisapride, erythromycin, pentamidine (when administered parenterally)
  - Sultoprid
  - Sparfloxacin

The combination of this medicine with the following drugs is GENERALLY NOT RECOMMENDED (see section 4.5):

- Beta-blockers and heart rate-lowering calcium channel blockers (verapamil, diltiazem);
- Stimulating laxative agents can cause hypokalemia and therefore increase the risk of *Torsade's de Pointes*.
- Fluoroquinolones
- Halofantrine, moxifloxacin

- Some neuroleptics (thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, amisulpride, tiapride, pimozide, haloperidol, droperidol)

In the case of cardiopulmonary resuscitation of shock-resistant ventricular fibrillation, none of the above contraindications apply.

4.4. Special warnings and precautions for use

Due to hemodynamic risks such as severe hypertension and circulatory collapse, direct i.v. administration is generally not recommended; Intravenous infusion should be preferred whenever possible.

Even if intravenous injection is done very slowly, it may aggravate hypotension, heart failure or severe respiratory failure.

Intravenous injection should only be reserved for emergencies and should be used in coronary intensive care units under continuous electrocardiographic control and blood pressure control if alternative treatments are insufficient.

Average dose is 5 mg / kg. The injection time should never be less than 3 minutes, except in the case of cardiopulmonary resuscitation of shock-resistant ventricular fibrillation. A second injection should not be given before 15 minutes after the first injection (even if only one ampoule has been administered) (risk of irreversible collapse).

It should not be mixed with any medication in the same syringe. When treatment needs to be continued, intravenous infusion should be used.

ECG and serum potassium measurements are recommended before starting treatment. During treatment, monitoring of transaminases and ECG recording are recommended.

Injectable amiodarone should be administered centrally. Administration by peripheral venous route may cause local effects such as superficial phlebitis. Injectable amiodarone should be administered as an infusion only.

It can reduce drop size when administered by infusion; infusion rate should be adjusted if necessary.

Caution should be exercised in cases of hypotension, severe respiratory failure, decompensated or severe heart failure.

The addition of amiodarone hydrochloride to the intravenous infusion solution decreases the drip volume, and this decrease increases as the concentration of amiodarone increases. The decrease in drop volume occurs because of the decrease in surface pressure of Tween 80 (polysorbate 80) added to the standard intravenous formulation. For changes in drop volume, a change in drop volume that results in reduced amiodarone hydrochloride uptake should be allowed.

Cardiac disorders:

It can significantly reduce heart rate in elderly patients.

If the dose is too high, it can cause severe bradycardia and conduction disturbances with the occurrence of idioventricular rhythm, especially in elderly patients or during digital therapy. In such cases, amiodarone therapy should be discontinued. If necessary, beta-adrenergic stimulants or glucagon can be administered. Because amiodarone has a long half-life, pacemaker implantation may be considered if bradycardia is severe and symptomatic.

Amiodarone is a potent CYP enzyme inhibitor. Therefore, it may lead to increased serum

concentrations of some drugs.
The prolongation of the QT interval is a result of the pharmacological properties of amiodarone. Therefore, the drug should not be used in patients with diagnosed or suspected congenital long QT syndrome and Torsades de Pointes.
CORDALİN may cause ECG changes. This "cordaronic" change causes prolongation of the QT interval due to the prolongation of repolarization. The accompanying U waves can be seen; this is an indication of the therapeutic effect of amiodarone, not toxicity.
Treatment should be discontinued if 2nd or 3rd degree A-V block, sinoatrial block or bifascicular block develops. Development of 1st degree atrioventricular block requires close follow-up.
The onset of new arrhythmias or worsening of treated arrhythmias, sometimes ending with death, have been reported. It is difficult to distinguish between drug ineffectiveness and having a proarrhythmic effect; however, it is important to understand whether this situation is related to the worsening of the current situation of the heart. Proarrhythmogenic effects have been reported less frequently with amiodarone compared to other antiarrhythmic agents and generally occur in the context of QT interval prolongation factors such as drug interactions and / or electrolyte disturbances (see section 4.5). Despite the prolongation of the QT interval, amiodarone exhibits low torsadogenic activity.
Neuromuscular disorders:
Amiodarone can cause peripheral sensorimotor neuropathy and / or myopathy. It usually resolves within a few months after stopping amiodarone therapy, but sometimes complete improvement may not be seen.
Eye disorders:
If blurred vision or reduced vision occurs, a complete ophthalmologic examination, including fundoscopy, is required immediately. It can cause optic neuropathy or optic neuritis. As a result, there may be weakness in vision.
Pulmonary disorders:
The onset of dyspnea or dry cough, alone or with impaired general condition, should suggest the possibility of pulmonary toxicity and a chest radiograph should be obtained (see section 4.8). When this diagnosis is suspected, a chest X-ray should be taken in patients who develop exertional dyspnea with or without impaired general health (weakness, weight loss, fever). In case of early discontinuation of amiodarone, interstitial pneumonia is usually reversible; In such cases, amiodarone therapy should be re-evaluated and corticosteroid therapy should be considered (clinical symptoms usually improve within 3-4 weeks, followed by a slower, radiological improvement and improvement in lung function tests within a few months). Some patients may get worse despite discontinuation of treatment. Cases of lung toxicity with a fatal outcome have been reported.
Severe cases of respiratory complications, sometimes fatal, have been observed very rarely and generally occurred immediately after surgery.
(adult acute respiratory distress syndrome); This may have been caused by a possible interaction with a high oxygen concentration, therefore careful observation of patients is recommended when administering artificial respiration to such patients (see sections 4.5 and 4.8).

Liver disorders:
Close monitoring of liver function tests (transaminases) is recommended regularly at the time of initiation of amiodarone and during treatment. Acute liver disorders (severe hepatocellular insufficiency or liver failure, sometimes fatal) or chronic liver disorders may occur within the first 24 hours of amiodarone iv administration and oral and intravenous forms. Therefore, if the level of transaminases exceeds three times the normal range, the amiodarone dose should be reduced or treatment discontinued.
The clinical or biological manifestations of chronic liver disorders due to oral amiodarone may be minimal (hepatomegaly, transaminase level up to 5 times the normal range) and may return when treatment is discontinued; however, cases that ended in death were reported.
Drug interactions:
It is not recommended to use Amiodarone in combination with beta blockers, calcium channel blockers that reduce heart rate (verapamil and diltiazem), stimulant laxative agents that can cause hypokalemia.
Increased plasma levels have been reported when flecainide was used in combination with amiodarone. Accordingly, the dose of flecainide should be reduced and the patient should be followed closely.
Tracing:
Electrolyte balance disturbances, especially hypokalaemia: Situations in which hypokalemia may accompany should be considered, as the proarrhythmic effect may favor the onset.
Hypokalaemia should be corrected prior to amiodarone administration.
In order to detect liver damage that may be caused by amiodarone, it is recommended that liver function (transaminase levels) be closely monitored as soon as amiodarone is initiated and regularly throughout the treatment period (see section 4.8). Acute liver disorders (including severe hepatocellular insufficiency or liver failure, which can sometimes be fatal) and chronic liver disorders may occur within the first 24 hours following iv amiodarone administration and during treatment with oral and intravenous forms. In this case, the dose of amiodarone should be reduced or treatment discontinued if transaminase levels exceed three times normal.
Since amiodarone may cause hypothyroidism or hyperthyroidism; Clinical and biological (USTSH) follow-up is recommended before starting amiodarone therapy, especially in patients with a personal history of thyroid disorders. This follow-up needs to be continued both during treatment and for several months after treatment is discontinued. When thyroid dysfunction is suspected, the serum hypersensitive TSH (usTSH) level should be measured. This follow-up needs to be continued both during treatment and for several months after treatment is discontinued. When thyroid dysfunction is suspected, the serum hypersensitive TSH (usTSH) level should be measured.
In particular, in the context of chronic antiarrhythmic drug use; There are cases reporting an increase in the rate-setting threshold of pacemaker or implantable cardioverter defibrillator and / or ventricular defibrillation; this potentially affects the efficacy of the drug. Therefore, it is recommended to reconfirm the functionality of such devices before and during amiodarone therapy.
Pediatric patients:
The safety and efficacy of amiodarone in pediatric patients has not been established. Because it

contains benzyl alcohol, its use is not recommended in pediatric patients under 3 years old.
Injectable amiodarone-containing ampoules contain benzyl alcohol (see section 4.3). Fatal cases of "Gasping syndrome" have been reported in newborns (less than 1 month old) following the administration of intravenous solutions containing this preservative. Striking symptoms such as hypotension, bradycardia and cardiovascular collapse can be seen at the onset of gasping syndrome.
Anesthesia:
Prior to surgery, the anesthesiologist should be warned that the patient has been treated with amiodarone.
Chronic treatment with amiodarone may increase the haemodynamic risks of general or local anesthetics in terms of side effects. These are, in particular, bardicardic and hypotensive effects, decreased cardiac output, and side effects related to conduction disturbances.

4.5. Interactions with other medical products and other forms of interaction

Many antiarrhythmic drugs can depress the heart's automatism, conduction system and contractility.
The combination of antiarrhythmics from different classes can provide a beneficial therapeutic effect, but it often requires VERY CAUTION; In this case, close clinical monitoring and ECG monitoring are essential. Combined use of antiarrhythmics (such as amiodarone) that cause torsades de Pointes is CONTRAINDICATED.
The combination of same class of antiarrhythmics is NOT recommended due to the increased risk of cardiac side effects, except in exceptional circumstances. Combined use with drugs that have negative inotropic, bradycardic and / or atrioventricular conduction slowing effects also requires CAUTION; In this case, close clinical monitoring and ECG monitoring should be done.
Since amiodarone has a long half-life, drug interactions may occur even months after amiodarone treatment is discontinued.
<u>Contraindicated in combination:</u>

- Drugs that cause Torsades de Pointes:
  - Class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide)
  - Class III antiarrhythmics (dofetilide, ibutilide, sotalol)
  - Other drugs: Bepridil, cisapride, diphemanil, i.v. erythromycin, mizolastine, i.v. vincamine, co-trimoxazole, or pentamidine injection
  - Sultopride
  - Some antipsychotics; chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride and sertindole
  - Tricyclic antidepressants such as lithium and doxepin, maprotiline, amitriptyline
  - Some antihistamines such as terfanadine, astemizole, mizolastine
  - Malaria drugs such as quinine, mefloquine, chloroquine, halofantrine
  - Moxifloxacin
- Sparfloxacin

  The risk of Torsades de Pointes increases due to prolongation of the QT interval (due to electrophysiological additive effects)

Not recommended in combination:

- Neuroleptics that cause Torsades de Pointes:

With certain phenothiazine neuroleptics (cyanamazine, levomepromazine, trifluoperazine), benzamide neuroleptics (sulpiride, tiapride), butyrophenone neuroleptics (droperidol), the risk of ventricular arrhythmia and especially Torsades de Pointes is increased.

- Stimulating laxative agents can cause hypokaliemia and therefore increase the risk of Torsades de Pointes.
- Injectable diltiazem:

There is a risk of bradycardia and atrioventricular block. If this combination needs to be given, continuous clinical monitoring and ECG monitoring are recommended.

- Beta-blockers (other than sotalol and esmolol):

Contractility, automatism, and conduction disorders may occur (due to suppression of compensatory sympathetic mechanisms).

- Fluoroquinolones:

QTc interval prolongation with or without Torsade de Pointes has been rarely reported in patients using amiodarone in combination with fluoroquinolones. The use of fluoroquinolones should be avoided in patients receiving amiodarone therapy.

Combinations to be used with caution:

- Drugs that prolong the QT interval:

Since the risk of Torsades de Pointes may be increased, the decision to use amiodarone with drugs known to prolong the QT interval should only be made after careful consideration of the potential risks and benefits for each patient and patients should be monitored for QT prolongation.

- General anesthetics:

Complications that can be serious have been reported in patients under general anesthesia: bradycardia (unresponsive to atropine), hypotension, conduction disturbances, decreased cardiac output.

Very rarely, severe respiratory complications (adult acute respiratory distress syndrome), which may sometimes result in death, have been observed usually immediately after surgery. This may be the result of interaction with high oxygen concentration.

- PgP substrates:

Amiodarone is a P-gp inhibitor. Combination with P-gp substrates is expected to result in an increase in exposure.

Dabigatran: Due to the risk of bleeding, caution should be exercised when using amiodarone with dabigatran. Dabigatran dosage may need to be adjusted according to product information.

- Oral anticoagulants:

Anticoagulant effect and hemorrhagic risk increase.

Prothrombin level and INR should be checked more frequently. The oral anticoagulant dose should be adjusted during amiodarone therapy and after treatment discontinuation.

- Drugs metabolized by the cytochrome P450 3A4 system:

Co-administration of such drugs with amiodarone, a CYP 3A4 inhibitor; This may lead to increased

plasma concentrations of these drugs and thus increased toxicity:

• Fentanyl: Combining with amiodarone may increase the risk of toxicity by enhancing the pharmacological effects of fentanyl.

• Statins: Concomitant use of amiodarone and statins metabolized by CYP 3A4, such as simvastatin, atorvastatin and lovastatin, increases the risk of muscle toxicity.

• It is recommended to use a statin that is not metabolised by CYP 3A4 in combination with amiodarone.

• Other drugs metabolized by CYP 3A4: Lidocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, colchicine.

– Flecainid:

Flecainide is mainly metabolized by CYP 2D6. Inhibition of this enzyme can increase plasma levels of amiodarone, flecainide; Therefore, it is recommended to reduce the dose of flecainide by 50% and to monitor the patient closely for side effects.

– Interactions with other CYP 450 isoenzyme substrates: In vitro studies also; showed that amiodarone also inhibits CYP1A2, CYP2C19 and CYP2D6 via its main metabolites. When administered together, amiodarone is expected to increase plasma concentrations of drugs whose metabolism is dependent on CYP1A2, CYP2C19 and CYP2D6.

– Cyclosporine:

Circulating cyclosporine levels increase due to decreased hepatic metabolism of the drug; There is a risk of nephrotoxic effects. Its dosage needs to be adjusted.

Measurement of blood cyclosporine concentrations, monitoring of renal function, and dose adjustment is necessary during amiodarone therapy and after treatment discontinuation.

– Oral diltiazem:

There is a risk of bradycardia and atrioventricular block, especially in the elderly.

Clinical follow-up and electrocardiographic monitoring should be done.

– Heart glycosides:

Automatism depression (excessive bradycardia) and atrioventricular conduction disorders can be seen. If digoxin is used, an increase in plasma digoxin levels may be observed due to decreased digoxin clearance. A synergistic effect on heart rate and atrioventricular conduction can also be seen.

Clinical monitoring and ECG monitoring should be done; If necessary, the dose of digoxin should be adjusted by measuring blood digoxin levels.

– Esmolol:

Contractility, automatism, and conduction disorders may occur (due to suppression of compensatory sympathetic mechanisms).

Clinical and electrocardiographic monitoring should be done.

– Potassium-lowering drugs:

Potassium-lowering diuretics (alone or in combination), stimulant laxatives, glucocorticoids (systemic use), tetracosactide, amphotericin B (i.v.)

Increased risk of ventricular arrhythmia and particularly Torsades de Pointes (hypokalaemia and / or hypomagnesemia is a predisposing factor). Other types of laxatives should be used.

Clinical follow-up and electrocardiographic monitoring should be done. Antiarrhythmic agents

should not be given if Torsades de Pointes occurs; Cardiac pacing can be initiated and i.v. magnesium can be used.

– Grapefruit juice:

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

– Phenytoin:

Increased plasma phenytoin levels and accompanying symptoms of especially neurological type overdose may be observed (due to decreased hepatic metabolism of phenytoin).

Clinical follow-up should be done, the plasma concentration of phenytoin should be checked and the dose of the drug adjusted if necessary.

– Bradycardic drugs:

Bradycardic calcium channel blockers (diltiazem, verapamil), beta-blockers (except sotalol), clonidine, guanfacine, cardiac glycosides, anticholinesterase drugs (donezepil, galantamine, rivastigmine, tacrine, ambemony, pyridostigmine, neostigmine).

Increased risk of ventricular arrhythmia, and especially Torsades de Pointes.

Electrocardiographic and clinical monitoring should be done.

– Simvastatin:

Increased risk of dose-dependent side effects such as rhabdomyolysis (due to reduced hepatic metabolism of cholesterol-lowering drug).

While applying simvastatin, the dose of 20 mg / day should not be exceeded.

If therapeutic efficacy cannot be achieved with this dose, another statin without such interaction should be used.

Additional information on special populations:

Pediatric population:

The efficacy and safety of amiodarone in children has not been established. Therefore, it is not recommended for use in children.

4.6. Pregnancy and lactation

General advice

Pregnancy category: D

Women with childbearing potential/Contraception

Women of childbearing potential should use appropriate contraception.

Pregnancy

Amiodarone has harmful pharmacological effects on pregnancy and / or fetus / newborn. No teratogenic effect was found in animal studies. Since no teratogenic effect is observed in animals, it is not expected to show a malformative effect in humans.

In fact, to date, the substances responsible for malformation formation in humans have been found to be teratogenic in animals, in studies conducted and properly conducted on both species.

Clinically, there is not enough data to evaluate the potential and malformative effect of amiodarone administered in the first trimester of pregnancy.

Since the fetal thyroid gland begins to bind iodine 14 weeks after the last menstrual period, no effect is expected on the fetal thyroid gland if the drug is administered before this period.

After this period, excessive iodine overload due to the use of the drug may cause biological or even clinical (goiter) hypothyroidism in the fetus.

Considering the effects of the fetus on the thyroid gland, as long as the benefits are not more than the risks; amiodarone is contraindicated during pregnancy.

Lactation

Amiodarone and its metabolite, together with iodine, pass into breast milk at higher concentrations than maternal plasma. Due to the risk of hypothyroidism in the newborn, breastfeeding is contraindicated during treatment with this drug.

The reproductive capability/Fertility

In fertility studies in which Amiodarone was administered to male and female rats at doses of 90 mg / kg / day, decreased fertility was observed. Amiodarone does not have a teratogenic effect. Amiodarone and desethylamiodarone pass into breast milk.

4.7. Effects on ability to drive and use machines

Based on the safety data on amiodarone, there is no evidence that amiodarone impairs the ability to drive or use machines.

4.8. Undesirable effects

The frequency of the adverse reactions listed below is defined according to the following explanation:

Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000), very rare (<1/10.000) and unknown (estimation based on the existing data is impossible).

Within each range grouping, undesirable effects are ranked in order of decreasing severity.

Blood and lymphatic system disorders

Very rare:	Thrombocytopenia, aplastic anemia, hemolytic anemia.
Unknown:	Granuloma, including bone marrow granuloma.

Immune system disorders

Very rare:	Anaphylactic shock.
Unknown:	Angioneurotic edema (Quincke's edema).

Endocrine diseases

Common:	Hypothyroidism and sometimes fatal when using the tablet form hyperthyroidism.
Very rare:	Syndrome of inappropriate antidiuretic hormone secretion.
Unknown:	Hyperthyroidism.

Cases of hyperthyroidism have been reported months after discontinuation of amiodarone therapy.

Psychiatric disorders

Unknown:	Anorexia.

Nervous system disorders:

Common:	Usually regressing after dose reduction or withdrawal extrapyramidal tremor; sleep disturbances, including nightmares.
Uncommon:	Sensory, motor or mixed peripheral neuropathy and myopathy, usually reversible upon discontinuation.
Very rare:	Ataxia of the cerebellar type, which usually regresses after dose reduction or withdrawal; intracranial hypertension (pseudo-tumor cerebri); headache; vertigo

In addition, dizziness, fatigue, memory weakness, and poor coordination have been reported.

Eye diseases

Very common:	Micro-deposits (usually limited to the area under the pupil); corneal micro-deposits.
Very rare:	Blurred vision; decrease in vision; optic neuropathy (optic neuritis), which may develop blindness with papillae edema at the bottom of the eye; the appearance of colored rings or blurred vision in intense light.

Cardiac diseases

Common:	Usually moderate and dose dependent bradycardia.
Uncommon:	Arrhythmia onset or worsening of pre-existing arrhythmias, sometimes followed by cardiac arrest; Conduction disturbances such as sinoatrial block and varying degrees of AV block.
Very rare:	Significant bradycardia and sinus arrest, necessitating discontinuation of amiodarone, especially in the elderly and / or patients with sinus node dysfunction
Not known:	Torsades de pointes

The arrhythmic effect of amiodarone is weaker than most antiarrhythmic agents and occurs in certain drug combinations (see section 4.5) and electrolyte imbalance.

Vascular diseases

Common: Moderate and transient drop in blood pressure; Severe cases of hypotension or circulatory collapse after excessively rapid administration or due to overdose.

Very rare: Hot flushes; vasculitis.

Respiratory, thoracic and mediastinal disorders

Common: Diffuse interstitial or alveolar pneumopathy; bronchiolitis obliterans organizing pneumonia (BOOP); Pleurisy, which often accompanies interstitial pneumopathies.

Very rare: Bronchospasm, especially in asthmatic cases; acute respiratory distress syndrome, sometimes fatal and sometimes immediately after surgery (with emphasis on the possibility of interaction with high doses of oxygen), usually associated with an interstitial pneumonia; bronchospasm and / or apnea, especially in asthmatics, severe respiratory failure; dyspnea on exertion.

Unknown: Pulmonary hemorrhage.

Gastrointestinal diseases

Very common: Nausea; vomiting; anorexia; constipation; Increase in AST or ALT levels; taste disturbances.

They usually occur during loading therapy and regress with dose reduction.

Hepato-biliary diseases

Very common: Usually moderate (1.5-3 times normal) increase in transaminase levels, which may regress even spontaneously with dose reduction.

Common: Acute hepatopathy associated with elevated serum transaminase levels and / or jaundice, sometimes fatal and requiring discontinuation of therapy.

Very rare: Cases of chronic hepatopathy seen during prolonged treatment (oral route). Histological appearance is similar to that of pseudo-alcoholic hepatitis. Uncertain clinical and laboratory findings (non-persistent hepatomegaly, serum transaminase level 1.5-5 times the normal level) require regular monitoring of liver function parameters. If elevation of serum transaminases - even moderately - occurs after more than 6 months of treatment, it should suggest chronic liver damage. Clinical and laboratory findings usually regress after discontinuation of treatment. Several cases have been reported that did not regress.

Skin and subcutaneous tissue disorders

Very common: Photosensitivity.

Common: Bluish or grayish pigmentations on the skin; It may occur with long-term and high-dose treatment and these pigmentations disappear gradually (10-24

months) after cessation of treatment.

Very rare: Sweating; erythema during radiotherapy; skin rashes; exfoliative dermatitis; alopecia.

Unknown: Urticaria.

Musculoskeletal and connective tissue disorders

Not known: Back pain.

Kidney and urinary tract diseases

Rare: Renal failure with moderate serum creatinine levels.

Reproductive system and breast diseases

Very rare: Epididymitis, impotence.

General disorders and administration site conditions

Common: Pain; erythema, edema; necrosis; extravasation; infiltration; inflammation; induration; thrombophlebitis, phlebitis; cellulite; infection; color changes.

Other side effects

Abnormal ability to smell

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose and treatment

There is no information regarding an overdose of amiodarone administered intravenously. Little is known about acute overdose of orally administered amiodarone. In a few cases, sinus bradycardia, heart block, ventricular arrhythmia - particularly Torsades de Pointes -, circulatory failure and liver impairment have been reported.

In case of overdose, symptomatic treatment should be given in addition to general supportive measures. The patient should be monitored; Beta-adrenergic stimulants or glucagon may be given in case of bradycardia. Spontaneously resolving ventricular tachycardia attacks may also occur. Due to the pharmacokinetic properties of amiodarone, the patient should be followed up for a sufficiently long time and especially for cardiac functions.

Amiodarone and its metabolites cannot be excreted by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antiarrhythmics: Class III
ATC Code: C01BD01

Amiodarone prolongs the 3rd phase of the action potential in cardiac muscle fibers, it does not change the rate or height of the ascension phase (Vaughan Williams Class III). The reason for the prolongation of only the 3rd phase of the action potential with amiodarone is that only the potassium current is slowed, with no change in sodium or calcium efflux.
Its bradycardic effect is due to the reduction of sinus automaticity; this effect is not antagonized by atropine.
It has an effect on non-competitive alpha and beta antiadrenergic receptors.
It causes a slowdown in sinoatrial, atrial and nodal conduction. This message increases with the heart rate.
It does not cause changes in intraventricular conduction.
It leads to an extension in the refractory period and a decrease in myocardial excitability at the atrial, nodal, and ventricular levels.
In atrioventricular side paths, it prolongs the refractory period and slows down the conduction.
It has no negative inotropic effect.
Also, for the use of amiodarone in cardiopulmonary resuscitation:
In patients with out-of-hospital cardiac arrest due to shock (defibrillator) resistant ventricular fibrillation,the safety and efficacy of i.v. amiodarone has been evaluated in two double-blind studies: the ARREST study (amiodarone-placebo comparison) and the ALIVE study (amiodarone-lidocaine comparison). The primary endpoint for both studies was survival to the hospital.
In the ARREST study, 504 patients who developed out-of-hospital cardiac arrest due to ventricular fibrillation or with three or more defibrillation shocks and epinephrine-resistant ventricular tachycardia, rapid injection of 300 mg amiodarone diluted in 20 ml of 5% dextrose into a peripheral vein (246 patients) or placebo (258 patients). Amiodarone significantly increased the chances of resuscitation and reaching the hospital in 197 patients (39%) who survived to the hospital: 44% in the amiodarone group and 34% in the placebo group ($p = 0.03$). After correcting for other independent factors determining the course of the disease, the adjusted Odds rate for survival to hospital arrival was 1.6 in the amiodarone group compared to the placebo group (95% confidence interval 1.1-2.4; $p = 0.02$). Hypotension (59% versus 25%; $p = 0.04$) or bradycardia (41% versus 25%; $p = 0.004$) occurred in more patients in the amiodarone group compared to the placebo group.
In the ALIVE study, 347 patients with recurrent ventricular fibrillation after three defibrillation shocks, epinephrine, and ventricular fibrillation resistant to a defibrillation shock again or after initial defibrillation, amiodarone (in 30 ml of 5% dextrose, at a dose of 5 mg / kg of estimated body weight) and lidocaine randomized to receive either placebo in view or placebo containing lidocaine (concentration 10 mg / ml, dose 1.5 mg / kg) and amiodarone in view of the same solvent (polysorbate 80). Amiodarone significantly increased the chance of resuscitation and reaching the hospital in 347 patients included in the study: 22.8% in the amiodarone group (41 out of 180

patients), 12% in the lidocaine group (20 out of 167 patients) [p = 0.009]. After correcting for other factors that could affect survival, the adjusted Odds rate for survival to hospital arrival was 2.49 in the amiodarone group compared to the lidocaine group (95% confidence interval 1.28-4.85; p = 0.007). There was no difference between the two treatment groups in the proportion of patients requiring atropine or dopamine pressor therapy for bradycardia, or openly applied lidocaine.
The proportion of patients who developed asystole after defibrillation following initial administration of the study drug was significantly higher in the lidocaine group compared to the amiodarone group (28.9% and 18.4%, respectively; p = 0.04).

5.2. Pharmacokinetic properties

General Particulars

Absorption:
It is not valid because of IV administration.

Distribution:
The effectiveness of the drug reaches its highest level within 15 minutes after injection and decreases in the following 4 hours.
Amiodarone is strongly bound to proteins.
High doses of amiodarone, eg 600 mg / day, should be administered so that effective tissue levels are reached as quickly as possible initially. Because of the long half-life of the drug, a maintenance dose of 200 mg / day, or even lower doses, is usually sufficient. Sufficient time should be waited for reaching the new balance of distribution between dose adjustments.

Biotransformation:
Amiodarone is mainly metabolized by CYP3A4 and CYP2C8. Amiodarone and its metabolite desethyl amiodarone have the potential to inhibit CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP2A6, CYP2B6 and 2C8 in vitro. Amiodarone and desethyl amiodarone also have the potential to inhibit P-gp and organic cation transporter (OCT2) (in one study, a 1.1% increase in the concentration of the OCT2 substrate creatinine was detected). In vivo data reveal the interactions of amiodarone with CYP3A4, CYP2C9, CYP2D6 and P-gp substrates.

Elimination:
Plasma half-life is generally about 50 days. However, this time can vary significantly from patient to patient. Patients with a half-life of less than 20 days or longer than 100 days have been reported. Its long half-life is life-saving in arrhythmias with mortality risk; Because of this property, occasional missed doses do not significantly affect the protection afforded by amiodarone.
Excretion from the kidneys is minimal, the main route of excretion is by faeces.

Characteristics in patients

Pediatric patients:
There are no controlled studies in children. In the limited published data on pediatric patients, no

significant difference compared to adults has been reported.

5.3. Preclinical safety data

Amiodarone has low acute toxicity. Following repeated administration, the toxicological profile is associated with hyperplastic and neoplastic changes, particularly characterized by thyroid hyperactivity in rats, characterized phospho lipidosis in rats and dogs, particularly the infiltration of foamy macrophages in the mesenteric lymph nodes and lungs, and photoallergy and phototoxicity in guinea pigs. Occasional increases in transaminase and alkaline phosphatase were observed in dogs as well as centrilobular hepatic congestion. Digestive disorders were also seen in these species.
Amiodarone is not teratogenic, but the toxic dose given to the mother animals reduces fertility and affects offspring development. Amiodarone and desethyl amiodarone pass into breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tween 80
Benzyl alcohol
Water for injection

6.2. Incompatibilities

The use of PVC materials or medical devices plasticized with DEHP [di (2-ethylhexyl) phthalate] may result in the release of DEHP in the presence of amiodarone solution for injection. In order to minimize the patient's exposure to DEHP, it is recommended that the final amiodarone dilution be prepared using DEHP-free kits prior to infusion.

6.3. Shelf life

24 months

6.4. Special precautions for storage

It should be stored at room temperature below 25 ° C, protected from light.

6.5. Nature and contents of container

Colorless, 3 mL Type I glass ampoules are presented in cardboard boxes (6 x 3 mL) containing 6 ampoules.

6.6. Special precautions for disposal and other handling

See. section 4.2
Due to its pharmaceutical properties, it should not be used at concentrations lower than 600 mg / liter.
Only 5% dextrose solution should be used.
Other preparations should not be mixed into the infusion solution.
The use of PVC materials or medical devices plasticized with DEHP [di (2-ethylhexyl) phthalate]

may result in the release of DEHP in the presence of amiodarone solution for injection. In order to minimize the patient's exposure to DEHP, it is recommended that the final dilution of amiodarone be prepared using DEHP-free hardware, -DEHP-free PVC, polyolefins (polyethylene, polypropylene), glass, etc. prior to infusion.
Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulations".

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

191/35

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

First Authorization Date: 05.05.1999
License renewal date: 11.05.2005

10. DATE OF REVISION OF THE TEXT