SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amiodarone 150 mg/3 ml Concentrate for Solution for Injection/Infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 ml ampoule contains 150 mg amiodarone hydrochloride.

Excipient with known effect
Benzyl alcohol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for Solution for Injection/Infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment should be initiated and normally monitored only under hospital or specialist supervision.
Amiodarone is indicated only for the treatment of severe rhythm disorders not responding to other therapies or when other treatments cannot be used:

- tachyarrhythmias associated with Wolff-Parkinson-White syndrome
- all other types of tachyarrhythmias including supraventricular, nodal and ventricular tachycardias; atrial flutter and fibrillation; ventricular fibrillation; when other drugs cannot be used.

Amiodarone can be used where a rapid response is required or where oral administration is not possible.

4.2 Posology and method of administration

Amiodarone should only be used when facilities exist for cardiac monitoring, defibrillation, and cardiac pacing. See section 6.6.

Amiodarone may be used prior to direct current (DC) cardioversion.

Posology

Adults

Infusion
Loading dose:
The standard recommended dose is 5mg/kg bodyweight given by intravenous infusion over a period of 20 minutes to 2 hours. This should be administered as a dilute solution in 250 ml 5% dextrose. This may be followed by repeat infusion up to 1200 mg (approximately 15 mg/kg bodyweight) in up to 500 ml 5% dextrose per 24 hours, the rate of infusion being adjusted on the basis of clinical response (see section 4.4).

The therapeutic effect is visible in the first minutes, then decreased gradually, and should be followed by a maintenance infusion.

Maintenance dose:
10 - 20 mg per kg bw in physiological glucose solution every 24 hours (on average 600 to 800 mg/ 24 hours up to a maximum of 1200 mg/ 24 hours accordingly 4-5 ampoules, maximum 8 ampoules) for a few days. On account of the stability of the solution, do not use concentrations below 300 mg per 500 ml and do not add other medicinal products to the infusion fluid.

To prevent local reactions (phlebitis), do not use concentrations exceeding 3 mg/ml. Repeated or continuous infusions via peripheral veins may lead to local reactions (inflammation).
Whenever repeated or continuous infusions are intended, administration via a central line is recommended.

Injection
In extreme clinical emergency, amiodarone may at the discretion of the clinician, be given as a slow injection of 150-300 mg (or 2.5 - 5 mg/kg) in 10-20 ml 5% glucose over a minimum of 3 minutes. This should not be repeated for at least 15 minutes. Patients treated in this way with Amiodarone must be closely monitored, e.g. in an intensive care unit (see section 4.4).

Method of administration
Amiodarone should be administered by a central venous route, except for cardiopulmonary resuscitation in case of cardiac arrest related to ventricular fibrillation resistant to defibrillation, where peripheral venous route could be used (see section 4.4).

Changeover from intravenous to oral use
As soon as an adequate response has been obtained (if possible, commence oral maintenance dose on the first day of the infusion), oral therapy should be initiated concomitantly at the usual loading dose (i.e. 200 mg three times a day). Amiodarone should then be phased out gradually.
In patients taking amiodarone concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/day (see sections 4.4, 4.5).

Paediatric population
The safety and efficacy of amiodarone in children has not been established.
Currently available data are described in sections 5.1 and 5.2.
Due to the presence of benzyl alcohol, amiodarone intravenous administration is contraindicated in neonates, infants and children up to 3 years old.

Elderly
As with all patients it is important that the minimum effective dose is used. Whilst there is no evidence that dosage requirements are different for this group of patients they may be more susceptible to bradycardia and conduction defects if too high a dose is employed. Particular attention should be paid to monitoring thyroid function (see sections 4.3, 4.4 and 4.8).

Cardiopulmonary resuscitation
Administration by a central venous catheter is recommended when it is immediately available. If not, the administration must be done by a peripheral venous route, using a large peripheral vein and with a flow as important as possible, or possibly, by a slow injection over a minimum of 3 minutes, followed by administration of 200 ml of infusion fluid. Do not give other medicinal substances in the same syringe with amiodarone. Amiodarone can cause severe irritation of the vein, therefore adequate rinsing after bolus injection must be ensured. In treatment of prolonged, refractory ventricular fibrillation, after administration of adrenaline and defibrillation, 300 mg as bolus injection and repeated, if necessary, with 150 mg bolus injection.

The recommended dose for ventricular fibrillations/pulseless ventricular tachycardia resistant to defibrillation is 300 mg (or 5 mg/kg body-weight) diluted in 20 ml 5% dextrose and rapidly injected. An additional 150 mg (or 2.5 mg/kg body-weight) IV dose may be considered if ventricular fibrillation persists.

Patients with liver and kidney problems
Although no dosage adjustment for patients with kidney or liver abnormalities has been defined during chronic treatment with oral amiodarone, close clinical monitoring is prudent for elderly patients.
For instructions on dilution of the sterile concentrate before administration, see section 6.6.

See section 6.2 for information on incompatibilities

4.3 Contraindications

- Known hypersensitivity to iodine or to amiodarone, or to any of the excipients listed in section 6.1 (one ampoule contains approximately 56 mg iodine)
- Sinus bradycardia, sino-atrial heart block. In patients with severe conduction disturbances (high grade AV block, bifascicular or trifascicular block) or sinus node disease, Amiodarone should be used only in conjunction with a pacemaker
- The combination of Amiodarone with drugs which may induce torsades de pointes is contra-indicated (see section 4.5)

- Severe respiratory failure, circulatory collapse, or severe arterial hypotension; hypotension, heart failure and cardiomyopathy are also contraindications when using Amiodarone as a bolus injection. However, these contraindications are not absolute and the use is allowed only under strict supervision with the greatest caution possible
- Evidence or history of thyroid dysfunction. Thyroid function tests should be performed where appropriate prior to therapy in all patients
- Due to the presence of benzyl alcohol, Amiodarone is contraindicated in neonates, infants and children up to 3 years old
- Pregnancy – except in exceptional circumstances (see section 4.6)
- Lactation. The use is allowed only in special life-threatening circumstances as specified in the second indication (see sections 4.1, 4.4 and 4.6).

Not all these above contra-indications apply to the use of amiodarone for cardiopulmonary resuscitation of shock resistant ventricular fibrillation.

4.4 Special warnings and precautions for use

Amiodarone Intravenous should only be used in a special care unit under continuous monitoring (ECG and blood pressure). IV infusion is preferred to bolus due to the haemodynamic effects sometimes associated with rapid injection (see section 4.8). Circulatory collapse may be precipitated by too rapid administration or overdosage (atropine has been used successfully in such patients presenting with bradycardia). Do not mix other preparations in the same syringe. Do not inject other preparations in the same line. If Amiodarone should be continued, this should be via intravenous infusion (see section 4.2).

Data of the SEARCH Study verify an increased risk of myopathy/rhabdomyolysis in combined use of amiodarone and simvastatin, which varies with the daily dose of simvastatin. The pharmacological mechanism on which this interaction is based is not known.

The indication for concomitant therapy of amiodarone with a statin should therefore be made with special caution. As no risk of myopathy/rhabdomyolysis is assumed only in case of a combined daily dose of amiodarone with simvastatin at low daily dose ≤ 20 mg, this simvastatin dose should not be exceeded. Other statins than simvastatin should be used at low dosage in concomitant therapy with amiodarone (see sections 4.2, 4.5).

Amiodarone may only be prescribed by competent specialists. Only to be used when other antiarrhythmics have shown insufficient effect. The patients must be monitored closely during treatment for radiological lungs examination, thyroid gland function and liver function test and ECG.

Amiodarone should only be used in a special care unit under continuous monitoring (ECG and blood pressure).

Administration of direct i.v. injections (bolus injections) is discouraged due to the risk of haemodynamic effects, such as serious hypotension and cardiovascular collapse. Such injections should only be used in an emergency - within a coronary intensive care unit and under ECG monitoring - when therapeutic alternatives have failed. Circulatory collapse may be precipitated by too rapid administration or overdosage (atropine has been used successfully in such patients presenting with bradycardia).

Its use should proceed with extreme caution - with haemodynamic monitoring - in patients with severe pulmonary impairment, arterial hypotension or stable congestive heart failure. Such patients should not be given a bolus injection (risk of exacerbation).

The proposed dose of 5 mg per kg, given as a direct injection, must not be exceeded.

If the effect of this product is too strong (e.g. severe bradycardia), appropriate measures should be taken, i.e. use of a pacemaker or beta stimulation.

The undiluted solution has not been adequately assessed for safety therefore, it is recommended not to use the solution for injection without prior dilution.

Repeated or continuous infusion via peripheral veins may lead to injection site reactions (see section 4.8). When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended.

When given by infusion amiodarone may reduce drop size and, if appropriate, adjustments should be made to the rate of infusion.

Anaesthesia (see section 4.5): Before surgery, the anaesthetist should be informed that the patient is taking amiodarone.

Cardiac disorders:
Caution should be exercised in patients with hypotension and decompensated cardiomyopathy and severe heart failure (also see section 4.3).

Amiodarone has a low pro-arrhythmic effect. Onsets of new arrhythmias or worsening of treated arrhythmias, sometimes fatal, have been reported. It is important, but difficult to differentiate a lack of efficacy of the drug from a proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects generally occur in the context of QT prolongation factors such as drug interactions and/or electrolytic disorders (see sections 4.5 and 4.8). Despite QT interval prolongation, amiodarone exhibits a low torsadogenic activity.

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

The pharmacological action of amiodarone induces ECG changes: QT prolongation (related to prolonged repolarisation) with the possible development of U-waves and deformed T-waves; these changes do not reflect toxicity. As with some other anti-arrhythmic agents, this phenomenon can lead to atypical ventricular tachycardias ("torsade de pointes") in exceptional cases.

Severe bradycardia (see section 4.5)

Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone is used in combination with sofosbuvir in combination with another hepatitis C virus (HCV) direct acting antiviral (DAA), such as daclatasvir, simeprevir, or ledipasvir. Therefore, coadministration 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 alone or in combination with other direct 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.

Primary graft dysfunction (PGD) post cardiac transplant:
In retrospective studies, amiodarone use in the transplant recipient prior to heart transplant has been associated with an increased risk of PGD.

PGD is a life-threatening complication of heart transplantation the presents as a left, right or biventricular dysfunction occurring within the first 24 hours of transplant surgery for which there is no identifiable secondary cause (see section 4.8). Severe PGD may be irreversible.

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

Respiratory, thoracic and mediastinal disorders (see section 4.8):
Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity such as interstitial pneumonitis. Very rare cases of interstitial pneumonitis have been reported with intravenous amiodarone. When the diagnosis is suspected, a chest X-ray should be performed. Amiodarone therapy should be re-evaluated since interstitial pneumonitis is generally reversible following early withdrawal of amiodarone, and corticosteroid therapy should be considered (see section 4.8). Clinical symptoms often resolve within a few weeks followed by slower radiological and lung function improvement. Some patients can deteriorate despite discontinuing amiodarone. Fatal cases of pulmonary toxicity have been reported.

Very rare cases of severe respiratory complications, sometimes fatal, have been observed usually in the period immediately following surgery (adult acute respiratory distress syndrome); a possible interaction with a high oxygen concentration may be implicated (see sections 4.5 and 4.8).

Hepato-biliary disorders (see section 4.8)

It is recommended to monitor hepatic function (transaminases) after initiation and during treatment with amiodarone.

Acute hepatic dysfunctions (including severe hepatocellular insufficiency or hepatic impairment, sometimes fatal) may occur, and also chronic hepatic dysfunctions, with the intravenous administration forms, within the first 24 hours of IV amiodarone, and may sometimes be fatal. Close monitoring of transaminases is therefore recommended as soon as amiodarone is started.

There may be clinical and biological signs of liver abnormalities due to chronic oral administration of amiodarone, which may be minimal (hepatomegaly, elevated transaminases 5 times above normal values) and reversible after discontinuation of treatment. However fatal cases were reported. Consequently, the amiodarone dose should be reduced or treatment discontinued if the transaminases increase exceeds three times the normal values.

Eye disorders (see section 4.8)
If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed. Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness.

Skin and subcutaneous tissue disorder (see section 4.8)
Exposure to sunlight should be avoided during therapy with amiodarone hydrochloride; this also applies to UV light applications and solaria. If this is not possible, uncovered skin parts, particularly the face, are to be protected by application of an ointment with a high protection factor. Even after withdrawal of amiodarone hydrochloride, a light protector is necessary for some more time.

Severe bullous reactions
Life-threatening or even fatal cutaneous reactions Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (see section 4.8). If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, amiodarone treatment should be discontinued immediately.

Endocrine disorders (see section 4.8)
Amiodarone IV may induce hyperthyroidism, particularly in patients with a personal history of thyroid disorders or patients who are taking/have previously taken oral amiodarone. Serum usTSH level should be measured when thyroid dysfunction is suspected.

Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T_3, free-T_4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of levothyroxine (T_4) to triiodothyronine (T_3) and may cause isolated biochemical changes (increase in serum free-T_4, free-T_3 being slightly decreased or even normal) in clinically euthyroid patients. There is no reason in such cases to discontinue amiodarone treatment if there is no clinical or further biological (usTSH) evidence of thyroid disease.

Due to the risk of developing a thyroid dysfunction (hyperthyroidism or hypothyroidism) during treatment with amiodarone hydrochloride, thyroid function should be examined prior to the onset of treatment. During therapy and up to one year after its withdrawal, these examinations should be repeated at regular intervals and the patients examined for clinical symptoms of hyperthyroidism or hypothyroidism.

Amiodarone hydrochloride inhibits the conversion 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 (euthyroid) patients without clinical symptoms. This findings constellation alone should not result in discontinuing therapy.

The clinical diagnosis of hypothyroidism is confirmed by proof of considerably increased ultrasensitive TSH value as well as decreased T_4 value. By proof of hypothyroidism, the amiodarone hydrochloride dosage should be reduced - if possible - and/or substitution with L-thyroxine started. In isolated cases, discontinuation of amiodarone hydrochloride may be required.

The clinical diagnosis of hyperthyroidism is confirmed by proof of considerably decreased ultrasensitive TSH as well as increased T_3 and T_4 values. By proof of hyperthyroidism, the dosage should be reduced - if possible - or amiodarone hydrochloride discontinued; in severe cases, treatment with thyroid depressants, beta-adrenergic blocking agents and/or corticosteroids should be initiated.

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

Nervous system disorders (see section 4.8):
Amiodarone may induce peripheral sensorimotor neuropathy and/or myopathy. Both these conditions may be severe, although recovery usually occurs within several months after amiodarone withdrawal, but may sometimes be incomplete.

Interactions with other medicinal products (see section 4.5)
Concomitant use of amiodarone with the following drugs is not recommended: beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem), stimulant laxative agents which may cause hypokalaemia.

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

After ending of the therapy there might be a still effective concentration of amiodarone in the blood serum for some weeks in case of a repeated intravenous administration because of the long half-life of amiodarone. After further subsidence of the amiodarone-level, arrhythmias can recur. Patients should be monitored regularly after ending of the therapy.

Paediatric population
Safety and efficacy of amiodarone hydrochloride in paediatric patients have not been established. Therefore its use in paediatric patients is not recommended, but if essential, the use is to be under the supervision of a paediatric cardiologist. No

controlled paediatric studies have been undertaken. In published uncontrolled studies effective doses for children were identified see (see section 4.2).

Important information about excipients
Amiodarone injection contains benzyl alcohol (20 mg/ml). Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children up to 3 years old. Increased risk due to accumulation in young children. Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates "Gasping Syndrome" (symptoms include a striking onset of gasping syndrome, hypotension, bradycardia and cardiovascular collapse). The minimum amount of benzyl alcohol at which toxicity may occur is not known. As benzyl alcohol may cross the placenta, solution for injection should be used with caution in pregnancy. High volumes should be used with caution and only if necessary, especially in subjects with liver, kidney impairment and in case of pregnancy and breastfeeding because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction with other medicinal products and other forms of interaction

In view of the long and variable half-life of amiodarone (approximately 50 days), potential for interactions with other medicinal products exists not only with concomitant medication but also with medicinal products administered after discontinuation of amiodarone.

Drugs inducing "Torsade de Pointes" or prolonging the QT interval
Some of the more important active substances that interact with amiodarone include oral anticoagulants warfarin, digoxin, phenytoin and any active substances which prolong the QT interval.

Combined therapy with the following drugs which prolong the QT interval is contra-indicated (see section 4.3 Contraindications) due to the increased risk of torsades de pointes; for example:

- Class Ia anti-arrhythmic drugs e.g. quinidine, procainamide, disopyramide
- Class III anti-arrhythmic drugs e.g. sotalol, bretylium, dofetilide and ibutilide
- intravenous erythromycin, co-trimoxazole (trimethoprim-sulfamethoxazole) or pentamidine injection
- some anti-psychotics e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride 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, lumefantrine
- gastrointestinal agents e.g. cisapride, droperidol
- Moxifloxacin.

CYP2C9 substrates
Amiodarone raises the plasma concentrations of CYP 2C9 substrates such as oral anticoagulants (warfarin) and phenytoin by inhibition of the cytochrome P450 2C9.

Oral anticoagulants (warfarin)

Amiodarone raises the plasma concentrations of oral anticoagulants (warfarin) by inhibition of CYP 2C9. The dose of anticoagulants (warfarin) should be reduced accordingly. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended.

Phenytoin
Similar to anticoagulants, by inhibition of CYP 2C9, amiodarone also interacts with phenytoin. Phenytoin dosage should be reduced if signs of overdosage appear, and plasma levels may be measured.

Digoxin
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; disturbances in automaticity (excessive bradycardia), a synergistic effect on heart rate and atrioventricular conduction may occur. Clinical, ECG and biological monitoring is recommended to observe for signs of digitalis toxicity and digoxin dosage 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 dosage of dabigatran as per its label.

Fluoroquinolones
There have been rare reports of QTc interval prolongation with or without torsade de pointes, in patients taking amiodarone with fluoroquinolones. Concomitant use of amiodarone with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contra-indicated, see above).

Drugs lowering heart rate, causing automaticity or conduction disorders
Combined therapy with the following active substances is not recommended:

- bradycardic active substances such as beta blockers, anticholinesterases (e.g. neostigmine) and certain calcium channel inhibitors (diltiazem, verapamil); potentiation of negative chronotropic properties and conduction slowing effects may occur
- Hypokalaemic active substances such as stimulant laxatives, diuretics, systemic corticosteroids, tetracosactide, intravenous amphotericin which may cause hypokalaemia and/or hypomagnesaemia thus increasing the risk of torsades de pointes; other types of laxatives should be used.

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, 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.

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

Cytochrome P450 3A4 substrates
When such medicinal products are co-administered with amiodarone, an inhibitor of CYP 3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity:

- Ciclosporin: plasma levels of ciclosporin may increase as much as 2-fold when used in combination. A reduction in the dose of ciclosporin may be necessary to maintain the plasma concentration within the therapeutic range
- Statins: the risk of muscular toxicity (e.g. rhabdomyolysis) is increased by concomitant administration of amiodarone with statins metabolised by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolised by CYP 3A4 when given with amiodarone
- Other drugs metabolised by cytochrome P450 3A4: examples of such drugs are lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine, ergotamine and colchine.

CYP 2D6 substrates

Flecainide
Given that flecainide is mainly metabolised by CYP 2D6, 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.

Interaction with substrates of other CYP 450 isoenzymes
In vitro studies show that amiodarone also has the potential to inhibit CYP 1A2, CYP 2C19 and CYP 2D6 through its main metabolite. When co-administered, amiodarone would be expected to increase the plasma concentration of drugs whose metabolism is dependent upon CYP 1A2, CYP 2C19 and CYP 2D6.

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 CYP 3A4 inhibitors (e.g. grapefruit juice and certain medicinal products) 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 drug interactions with amiodarone (see section 4.4)
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 section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies are available. Amiodarone and N-desmethylamiodarone cross the placental barrier and achieve 10-25% of the maternal plasma concentrations in the infant. Most frequent complications include impaired growth, preterm birth and impaired function of the thyroid gland in newborn babies. Hypothyroidism, bradycardia and prolonged QT intervals were observed in approximately 10 % of the newborn babies. In isolated cases an increased thyroid gland or cardiac murmurs were found. The malformation rate does not appear to be increased. However, the possibility of cardiac defects should be kept in mind. Therefore, Amiodarone must not be used during pregnancy unless clearly necessary and the real risk of reoccurrence of life threatening arrhythmias should be weighed against the possible hazard for the fetus. Given the long half-life of amiodarone, women of child-bearing age would need to plan for a pregnancy starting at least half a year after finishing therapy, in order to avoid exposure of the embryo/fetus during early pregnancy.

Breastfeeding
The passage into mother’s milk is proven for the active ingredient and for the active metabolite. If therapy is required during the lactation period, or if Amiodarone was taken during pregnancy, breast-feeding should be stopped.

Fertility
Elevated serum levels of LH and FSH were found in male patients after long-term treatment indicating testicular dysfunctions.

4.7 Effects on ability to drive and use machines

There are no known data available. As blurred and/or reduced vision may occur, a possible effect on the ability to drive and use machines should be considered.

4.8 Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of MedDRA frequency convention: very common (≥1/10), common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000), very rare (<1/10000); Not known (cannot be estimated from available data).

Blood and lymphatic systems disorders
In patients taking amiodarone there have been incidental findings of bone marrow granulomas. The clinical significance of this is unknown.
Not known:
- neutropenia, agranulocytosis

Endocrine disorders *(see section 4.4):*
Common:
- hypothyroidism
- hyperthyroidism, sometimes fatal

Very rare:
- syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Eye disorders *(see section 4.4):*
Very common:
- micro-deposits at the anterior surface of the cornea are found in almost every patient, which are usually limited to the area below the pupil. They may be associated with colored halos in dazzling light or blurred vision. They usually regress 6-12 months after discontinuation of amiodarone hydrochloride

Very rare:
- optic neuropathy/neuritis that may progress to blindness (see section 4.4)

Cardiac disorders:
Common:
- bradycardia, generally moderate

Very rare:
- marked bradycardia, sinus arrest requiring discontinuation of amiodarone, especially in patients with sinus node dysfunction and/or in elderly patients
- onset of worsening of arrhythmia, sometimes followed by cardiac arrest (see sections 4.4 and 4.5)

Not known:
- Torsades de pointes (see 4.4 and 5.1)

Gastrointestinal disorders:
Very rare:
- nausea

Not known:
- pancreatitis (acute)

General disorders and administration site conditions:
Common:
- injection site reactions such as pain, erythema, oedema, necrosis, extravasation, infiltration, inflammation, induration, thrombophlebitis, phlebitis, cellulitis, infection, pigmentation changes

Hepato-biliary disorders:
Very rare:
- isolated increase in serum transaminases, which is usually moderate (1.5 to 3 times normal range) at the beginning of therapy. They may return to normal with dose reduction or even spontaneously
- acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, sometimes fatal (see section 4.4)

Immune system disorders:
Rare:
- the excipient benzyl alcohol may cause hypersensitivity reactions

Very rare:
- anaphylactic shock

Not known:
- angioneurotic oedema (Quincke's Oedema)

Nervous system disorders:
Common:
- extrapyramidal tremor, for which regression usually occurs after reduction of dose or withdrawal

Uncommon:
- peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the drug (see section 4.4)
- dizziness

Very rare:
- cerebellar ataxia, for which regression usually occurs after reduction of dose or withdrawal
- benign intracranial hypertension (pseudo-tumor cerebri)
- headache
- vertigo

Psychiatric disorders:
Common:
- nightmares
- sleep disorders

Not known:
- hallucinations
- delirium (including confusion)

Musculoskeletal and connective tissue disorders:
Common:
- muscle weakness

Not known:
- back pain

Respiratory, thoracic and mediastinal disorders:
Very rare:
- interstitial pneumonitis or fibrosis, sometimes fatal (see section 4.4)

- severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal (see sections 4.4 and 4.5)
- bronchospasm and/or apnoea in case of severe respiratory failure, and especially in asthmatic patients.

Skin and subcutaneous tissue disorders:

Very common:
- photosensitivity (see section 4.4).

Common:
- eczema
- slate grey or bluish pigmentations of light-exposed skin, particularly the face, in case of prolonged treatment with high daily dosages; such pigmentations slowly disappear following treatment discontinuation.

Very rare:
- sweating
- erythema during the course of radiotherapy
- skin rashes, usually non-specific
- exfoliative dermatitis.

Not known:
- urticaria
- severe skin reactions (sometimes fatal) such as toxic epidermal necrolysis (TEN)/Stevens- Johnson syndrome (SJS), bullous dermatitis and Drug reaction with eosinophilia and systematic symptoms (DRESS).

Vascular disorders:

Common:
- decrease in blood pressure, usually moderate and transient. Cases of hypotension or collapse have been reported following overdosage or a too rapid injection.

Very rare:
- hot flushes

Injury, poisoning and procedural complaints
- Not known: Primary graft dysfunction post cardiac transplant (see section 4.4)

Reproductive system and breast disorders

Not known:
- libido decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no information regarding overdosage with intravenous amiodarone.

Little information is available regarding acute overdosage with oral amiodarone. Few cases of sinus bradycardia, heart block, attacks of ventricular tachycardia, torsades de pointes, circulatory failure and hepatic injury have been reported.

In the event of overdose, treatment should be symptomatic, in addition to general supportive measures.

The patient should be monitored and if bradycardia occurs beta-adrenostimulants or glucagon may be given.

Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of amiodarone, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended.

Neither amiodarone nor its metabolites are dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 3.2.3. Cardiovascular apparatus. Antiarrhythmic, Repolarization lengtheners (Class III); ATC code: C01BD 01

Amiodarone is a di-iodinated benzofuran derivative and is classified as a class III antiarrhythmic agent owing to its ability to increase the cardiac action potential duration in both atrial and ventricular myocytes via block of cardiac K^+ channels (mainly of the rapid component of the delayed rectifier K^+ current, I_{Kr}). Thus, it prolongs the refractory period of the action potential leading to depression of ectopies and re-entry-arrhythmias and to prolongation of the QT_c interval in the ECG. Furthermore, Amiodarone also blocks cardiac Na^+ currents (class I effect) and Ca^{2+} currents (class IV effect). The latter may lead to slowing of conduction through the sinoatrial and atrioventricular nodes. During long-term administration, Amiodarone also seems to inhibit the trafficking of ion channels from the endoplasmic reticulum to the plasma membrane in cardiac myocytes, and these effects may contribute to the cardiac electrophysiological actions of Amiodarone under chronic administration. Furthermore, Amiodarone is a non-competitive antagonist at both ß- and α-adrenoceptors and, therefore, has haemodynamic effects: dilatation of coronary arteries and peripheral vasodilation leading to a reduction of systemic blood pressure. Negative inotropic, negative chronotropic and negative dromotropic effects seem to be induced by the ß-adrenergic antagonistic effects induced by Amiodarone. Some effects of Amiodarone are comparable with hypothyroidism, which might be due to inhibition of thyroid hormone synthesis. Amiodarone is a potent inhibitor of iodothyronine-5´-monodeiodinase activity (the main T4-T3 converting enzyme). In rats, increases in serum thyroid-stimulating hormone (TSH), thyroxine (T4) and reverse triiodothyronine (rT3), and decreases in serum triiodothyronine (T3) as a result of inhibition of deiodination of T4 to T3 have been observed. These antithyroid actions of Amiodarone might contribute to its cardiac electrophysiological effects. The main metabolite N-desethylamiodarone has effects on cardiac electrophysiology similar to those of the parent compound

Cardiopulmonary resuscitation in case of cardiac arrest related to ventricular fibrillation resistant to defibrillation

The safety and efficacy of IV amiodarone in patients with cardiac arrest, in hospital, due to ventricular fibrillation resistant to defibrillation were evaluated in two double blinded clinical trials: the ARREST study, that compares amiodarone with placebo, and the ALIVE study, that compares amiodarone with lidocaine. The primary endpoint of both trials was the survival after hospital admission.

In the ARREST study, there were randomized 504 patients with cardiac arrest in hospital due to ventricular fibrillations/pulseless ventricular tachycardia resistant to three or more defibrillation and adrenaline, of which 246 patients received 300mg of amiodarone diluted in 20ml 5% dextrose by bolus injection in peripheral vein, and 258 patients with placebo. From the 197 patients that survived (39%), amiodarone increased significantly the resuscitation scenario and inpatient hospital: 44% in the group of amiodarone and 34% in the group of placebo, respectively (p=0.03). After amendment of other outcome predictors, the adjusted ratio of the likelihood of survival at hospital admission in the group of amiodarone compared to the placebo group was 1.6 (95% confidence interval, 1.1 to 2.4; p=0.02). There were more patients with hypotension in the group treated with amiodarone than in placebo's group (59% vs 25%, p=0.04) or with bradycardia (41% vs 25%, p=0.004).

In the ALIVE study, there were randomized 347 patients with ventricular fibrillation resistant to three electric defibrillations, adrenaline and another electric defibrillation, or with recurrent ventricular fibrillation after successful initial defibrillation, some with amiodarone (5mg/kg at a 10mg/ml concentration) and placebo corresponding to lidocaine, or with lidocaine (1.5mg/kg at a 10mg/ml concentration) and placebo corresponding to amiodarone with the same diluent (polysorbate 80). From the 347 patients included, it was established that amiodarone increased the resuscitation scenario and inpatient hospital: 22.8% in the amiodarone's group (41 patients from 180) and 12% in the lidocaine group (20 patients from 167), p=0.009. After adjustment to other factors that may affect the likelihood of survival, the adjusted ratio of the survival likelihood to hospital admission in the group of amiodarone, when compared with the group of lidocaine was 2.49 (95% confidence interval, 1.28 to 4.85; p=0.007). There were no differences between the two groups concerning the percentage of patients who needed medication for bradycardia, with atropine or vasoconstrictor treatment with dopamine, not either concerning the percentage of patients receiving open lidocaine. The percentage of patients that had asystole as a consequence of the defibrillation after the administration of the initial treatment was significantly higher in the group of lidocaine (28,9%) than in the group of amiodarone (18.4%), p=0.04.

The proportion of patients in whom asystole occurred following defibrillation shock after administration of the initial study drug was significantly higher in the lidocaine group (28.9%) than in the amiodarone group (18.4%) , p = 0.04.

Paediatric population
No controlled paediatric studies have been undertaken.

In published studies the safety of amiodarone was evaluated in 1118 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 dosage 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)

Intravenous

- Loading dose: 5 mg/kg body weight over 20 minutes to 2 hours
- Maintenance dose: 10 to 15 mg/kg/day from few hours to several days

If needed oral therapy may be initiated concomitantly at the usual loading dose.

5.2 Pharmacokinetic properties

Pharmacokinetics of amiodarone are unusual and complex, and have not been completely elucidated.

Absorption
Absorption following oral administration is variable and may be prolonged, with enterohepatic cycling.

Distribution
Amiodarone is highly protein bound > 95%).
A study in both healthy volunteers and patients after intravenous administration of amiodarone reported that the calculated volumes of distribution and total blood clearance using a two-compartment open model were similar for both groups.
The very high volume of distribution combined with a relatively low apparent volume for the central compartment suggests extensive tissue distribution. A bolus IV injection of 400 mg gave a terminal T½ of approximately 11 hours.

Biotransformation
The major metabolite is desethylamiodarone.
Amiodarone and desethylamiodarone exhibit a potential *in vitro* to inhibit CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP2A6, CYP2B6 and CYP 2C8. They also have a potential to inhibit some transporters such as P-gp and organic cation transporter (OCT2) (One study shows a 1.1% increase in concentration of creatinine (an OCT 2 substrate). *In vivo* data describe amiodarone interactions on CYP3A4, CYP2C9, CYP2D6 and P-gp substrates.

Elimination
Renal excretion is minimal and faecal excretion is the major route.
Elimination of amiodarone after intravenous injection appeared to be biexponential with a distribution phase lasting about 4 hours.

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.

5.3 Preclinical safety data

In chronic toxicity studies, amiodarone led to pulmonary damage (fibrosis, phospholipidosis; in hamsters, rats and dogs). Pulmonary toxicity appears to result from radical formation and perturbation of cellular energy production. In addition, amiodarone caused liver damage in rats.

Regarding the genotoxicity aspects the in vitro Ames test and in vivo mouse bone marrow micronucleus test have been conducted. Both studies yielded negative results.

In a 2-year carcinogenicity study in rats, amiodarone caused an increased incidence of thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinical relevant exposures. Since mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is proposed for this type of tumour induction. In the mouse, carcinomas were not observed, but a dose-dependent thyroid follicular hyperplasia was seen. These effects on the thyroid in rats and mice are most likely due to effects of amiodarone on the synthesis and/or release of thyroid gland hormones. The relevance of these findings to man is low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80, Benzyl alcohol, Hydrochloride acid or Sodium Hydroxide, Water for injection

6.2 Incompatibilities

The use of administration equipment or devices containing plasticizers such as DEHP (di-2-ethylhexylphthalate) in the presence of amiodarone may result in leaching out of DEHP. In order to minimise patient exposure to DEHP, the final amiodarone dilution for infusion should preferably be administered through non DEHP-containing sets.

See section 6.6, “Special precautions for disposal and other handling”

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

Do not refrigerate or freeze. Storage at low temperature may cause the formation of precipitate. Do not use unless solution is clear.

Store in the original container.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.5 Nature and contents of container

Each carton contains 5 or 10 glass ampoules.

6.6 Special precautions for disposal

Amiodarone is incompatible with saline and should be administered solely in 5% dextrose solution. Amiodarone diluted with 5% dextrose solution to a concentration of less than 0.6 mg/ml is unstable. Solutions containing less than two ampoules Amiodarone in 500 ml dextrose 5% are unstable and should not be used.

For single dose use only. Discard any unused solution immediately after initial use.

The dilution is to be made under aseptic conditions. Before use, the sterile concentrate should be visually inspected for clarity, particulate matter, discolouration and the integrity of the container. The solution should only be used if it is clear, free from particles and the container is undamaged and intact.

Prior to administration by intravenous infusion, Amiodarone should be diluted according to directions with the recommended infusion fluid, 5% w/v Glucose Intravenous Infusion. The contents of one ampoule of the sterile concentrate diluted as recommended in 250 ml of 5% w/v Glucose Intravenous infusion contains 0.6 mg/ml of Amiodarone.

Solutions containing less than 300 mg of amiodarone (two ampoules) in 500 ml of 5% w/v Glucose Intravenous Infusion are not stable and must not be used. It should also be stressed that no other compounds are to be mixed with amiodarone infusion solution.

Amiodarone should be administered solely in 5% w/v Glucose Intravenous Infusion.

Amiodarone must not be mixed with other medicinal products in the same syringe.

Intravenous infusion:

The calculated dose is diluted with 250 ml 5% w/v Glucose Intravenous Infusion. See section 4.2.

Intravenous injection:

150-300 mg (corresponding to 3-6 ml Amiodarone) is diluted with 10-20 ml 5% w/v Glucose Intravenous Infusion. See section 4.2.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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04011 Aprilia (LT)

Italy

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