Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amiodarone hydrochloride 30 mg/ml concentrate for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 30 mg amiodarone hydrochloride.

Each syringe of 10 ml contains 300 mg amiodarone hydrochloride.

Excipient with known effect
Each syringe contains

- 20 mg/ml of benzyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection/infusion

Clear colourless to pale yellow solution, practically free from particulates.

pH 3.0-5.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Amiodarone hydrochloride is indicated for the treatment of adult patients with:

- Serious, symptomatic, tachycardic ventricular arrhythmias.

Symptomatic tachycardic supraventricular arrhythmias requiring treatment, such as

- AV junctional tachycardia,
- Supraventricular tachycardia in Wolff-Parkinson-White syndrome or
- paroxysmal atrial fibrillation.

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

Treatment should be initiated and normally monitored only under hospital or specialist supervision.

The injection solution can normally only be used in a hospital, when a rapid response is required or when oral administration is not possible. The injection solution must only be used to initiate therapy.

4.2 Posology and method of administration

Posology

For ***attack or initial treatment***, intravenous injection or intravenous infusion is possible. Intravenous injection is generally not recommended. Whenever possible, intravenous infusion should be preferred (see also section 4.4).

Intravenous infusion

*Initial or attack 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 250ml 5% dextrose.

Therapeutic effects can be observed within a few minutes and then gradually diminish. Therefore, the therapy should be continued with a maintenance infusion.

Maintenance dose: Infuse up to 1200mg (10-20 mg/kg bodyweight) in 250-500ml 5% dextrose per 24 hours; the rate of infusion being adjusted on the basis of clinical response (see section 4.4).

Changeover from Intravenous to Oral therapy
As soon as an adequate response has been obtained, oral therapy should be initiated concomitantly at the usual loading dose. Amiodarone hydrochloride should then be phased out gradually.

Intravenous injection (see section 4.4)
In extreme clinical emergency, the drug may, at the discretion of the clinician, be given as a slow injection of 150 – 300 mg (5 mg/kg of bodyweight) in 10-20ml 5% dextrose over a minimum of 3 minutes. This should not be repeated for at least 15 minutes, even if the maximum dose was not given at the first injection. Patients treated in this way with amiodarone must be closely monitored, e.g. in an intensive care unit (see section 4.4).

Cardiopulmonary resuscitation in the treatment of defibrillation-resistant ventricular fibrillation: The initial IV dose is 300 mg (or 5 mg/kg) diluted in 20 ml of 5% dextrose, and injected rapidly. An additional IV dose of 150 mg (or 2.5 mg / kg) should be considered if ventricular fibrillation persists.

Paediatric population:
The safety and efficacy have not been established in children. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Due to the presence of benzyl alcohol, intravenous amiodarone must not be used in premature infants, neonates, infants and children up to 3 years old. (see section 4.3).

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).

Hepatic and renal impairment
Although no dosage adjustment for patients with renal or hepatic abnormalities has been defined during chronic treatment with oral amiodarone, close clinical monitoring is prudent for elderly patients e.g. in an intensive care unit.

Method of administration
For **intravenous infusions**, amiodarone must **be diluted** as per instructions above before use.

For slow **intravenous injections** (during clinical emergencies only), amiodarone **must be diluted** further with 10 or 20 ml of dextrose 5% depending on the dose administered and the indication. E.g. For cardiopulmonary resuscitation, dilute the content of one syringe (300mg/ 10ml) further with 20ml dextrose 5%.

For single use only.

Only 5% dextrose solution may be used for infusion (see sections 6.2).

For instructions on dilution of the product before administration, see section 6.6.
To avoid phlebitis, a central venous catheter should be placed during continuous infusion.
Amiodarone Injection Solution is normally only administered to initiate therapy, not for longer than one week.

4.3 Contraindications

- Hypersensitivity to the active substance, iodine or to any of the excipients listed in section 6.1 (one syringe contains approximately 112 mg iodine).
- Sinus bradycardia and 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 specialized units in conjunction with a pacemaker.
- Patients with Brugada syndrome.
- Evidence or history of thyroid dysfunction. Thyroid function tests should be performed where appropriate prior to therapy in all patients.
- Severe respiratory failure, circulatory collapse, or severe arterial hypotension; hypotension, heart failure and cardiomyopathy are also contra-indications when using amiodarone as a bolus injection.
- The combination of amiodarone with drugs which may cause torsades de pointes arrhythmia (see section 4.5).
- Pre-existing QT prolongation
- Hypokalemia
- History of Angioneurotic edema (hereditary or idiopathic, e.g. as a result of previous amiodarone therapy),
- Simultaneous treatment with MAO inhibitors
- Due to the presence of benzyl alcohol, intravenous amiodarone is contraindicated in in premature infants, neonates, infants and children up to 3 years old.
- Pregnancy: only in exceptional circumstances and unless clearly necessary (see section 4.6)
- Breastfeeding (see section 4.6).

All these above contra-indications do not apply to the use of amiodarone for cardiopulmonary resuscitation in the treatment of defibrillation-resistant ventricular fibrillation.

4.4 Special warnings and precautions for use

See also section 4.3.

IV injection is generally discouraged because of hemodynamic risks (severe hypotension, circulatory collapse); therefore, whenever possible, administration by intravenous infusion is preferable.

The IV injection should be limited to emergency situations when other therapeutic alternatives have failed. It should only be used in intensive care units and under continuous monitoring (ECG, blood pressure).

The dosage is approximately 5 mg/kg of body mass. Except in cardiopulmonary resuscitation in the treatment of defibrillation-resistant ventricular fibrillation, amiodarone must be injected in a minimum time of 3 minutes and a second intravenous injection must not be administered before 15 minutes after the first injection, even if the maximum dose was not given at the first injection. (risk of irreversible collapse).

Other preparations should not be mixed in the same syringe. Do not administer other preparations on the same line. If the treatment should be prolonged, this should be done by intravenous infusion (see section 4.2).

Cardiac disorders:

- Sinus bradycardia may occur, which can be more severe in elderly patients or in patients with impaired sinus node function.
- Treatment should be interrupted in case of severe bradycardia or heart block.
- As a consequence of the proarrhythmogenic effects of amiodarone, new arrhythmias or worsening episodes of the treated arrhythmias have been reported, with fatal outcome in some cases. In these cases, the need for withdrawal from treatment with amiodarone should be assessed. It is also important, although difficult, to differentiate the lack of efficacy of the medication, from a proarrhythmic effect, whether or not it is associated with the worsening of the heart condition. Proarrhythmic effects are reported more rarely with amiodarone than with other antiarrhythmics and generally occur in the context of factors that prolong the QT interval such as drug interactions

and / or electrolyte disorders (see section 4.5 and 4.8). Despite the prolongation of the QT interval, amiodarone shows low torsadogenic activity.

- During long-term therapy (e.g. after switch to oral therapy), cardiological check-ups should be carried out at regular intervals during treatment (e.g. at intervals of one month with a standard ECG or three months with a long-term ECG and, if necessary, exercise ECG). If individual parameters deteriorate, e.g., if the QRS time or QT time is extended by more than 25%, or the PQ time by more than 50%, or QT is prolonged to more than 500 ms, or an increase in the number or severity of cardiac arrhythmias is observed, therapy should be re-evaluated.

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 that 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.

Severe bradycardia and heart block (see section 4.5):

Life-threatening cases of bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone.

Bradycardia has generally occurred within hours to days, but later cases have been mostly observed up to 2 weeks after initiating HCV treatment.

Amiodarone should only be used in patients on sofosbuvir- containing regimen when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated.

Should concomitant use of amiodarone be considered necessary, it is recommended that patients undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Due to the long half-life of amiodarone, cardiac monitoring as outlined above should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofosbuvir containing regimen.

All patients receiving amiodarone in combination with sofosbuvir-containing regimen should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

Hyperthyroidism and Hypothyroidism:
Hyperthyroidism may occur during therapy or up to a few months after stopping amiodarone therapy. The following, usually mild symptoms should be considered by the doctor:
Weight loss, tachycardia, tremor, nervousness, increased sweating and heat intolerance, recurrence of arrhythmias or angina pectoris, heart failure.

The clinical diagnosis of hyperthyroidism is confirmed by evidence of a significantly reduced ultrasensitive TSH and increased T_3 and T_4 values.

If hyperthyroidism is demonstrated, Amiodarone hydrochloride treatment should be discontinued. An improvement occurs within a few months after stopping treatment and is accompanied by a normalization of the thyroid function tests.

In severe cases (some fatal), individual emergency treatment with antithyroid drugs, beta-blockers and/or corticosteroids must be started.

Thyroid gland:
Because of the risk of developing thyroid dysfunction (hyper- or hypothyroidism) during Amiodarone hydrochloride treatment, thyroid function tests should be performed before starting treatment.

During the therapy and up to about a year after discontinuation of the therapy, these examinations should be repeated at regular intervals and the patients examined for clinical signs of hyper- or hypothyroidism.

Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function test (free- T_3, free T_4 , usTSH) remain interpretable. Amiodarone inhibits the conversion of thyroxine (T_4) to triiodothyronine (T_3) and can lead to increased T4 values and reduced T3 values in clinically unremarkable (euthyroid) patients. This constellation of findings alone should not lead to therapy being discontinued.

The following symptoms may indicate hypothyroidism:
Weight gain, sensitivity to cold, fatigue, an extreme bradycardia beyond the effects to be expected with Amiodarone hydrochloride treatment.

The clinical diagnosis of hypothyroidism is confirmed by evidence of a significantly increased ultrasensitive TSH and a reduced T_4. Euthyroidism usually occurs within 1–3 months of stopping treatment.

If hypothyroidism is demonstrated, the amiodarone dose should be reduced if possible and/or levothyroxine substitution should be started. In some cases, Amiodarone hydrochloride treatment may need to be discontinued.

Pulmonary disorders:

- The onset of dyspnea or nonproductive cough may be related to lung toxicity such as interstitial pneumonitis or hypersensitivity pneumonitis.
- Therefore, a chest X-ray and a pulmonary function test should be performed prior to treatment initiation, if possible. During the course of a long-term therapy (e.g., after switching to oral amiodarone), these examinations should be repeated at intervals of 3-6 months. In patients with severe pulmonary diseases, the pulmonary function should be examined more frequently, since these patients have a worse prognosis in case of amiodarone-induced lung toxicity.
- Very rarely, cases of interstitial pneumonitis with intravenous amiodarone have been reported.
- In patients who develop signs of lung toxicity like isolated dyspnea on exertion or associated with a general deterioration of health status (fatigue, weight loss, fever), a chest x-ray should be performed.
- In cases of interstitial pneumonitis, treatment with amiodarone should be reassessed since interstitial pneumonitis is usually reversible after early withdrawal of amiodarone (clinical signs usually resolve within 3 or 4 weeks, followed by a slow radiological improvement and lung function in several months, and corticosteroid therapy should be considered (see section 4.8).
- In cases of hypersensitivity pneumonitis, amiodarone therapy should be stopped, and a therapy with corticosteroids should be initiated.
- Very rare cases of serious respiratory complications, sometimes fatal, have been observed, usually in the period immediately after surgery (adult acute respiratory distress syndrome); a possible interaction with a high oxygen concentration may be involved (see section 4.5 and section 4.8).

Hepatic disorders (see section 4.8):

- As soon as treatment with amiodarone is started and regularly during therapy, close monitoring of liver function tests (transaminases) is recommended.
- During oral or intravenous administration , acute liver disorders (including severe hepatocellular failure or sometimes fatal liver failure) and chronic liver disorders may occur (in case of intravenous administration already within the first 24 hours). Therefore, the dose of amiodarone should be reduced or treatment discontinued if the increase in transaminases exceeds three times the reference values.
- The clinical and biological signs of chronic liver disorders due to oral administration of amiodarone may be minimal (cholestatic jaundice, hepatomegaly, transaminases increased up to 5 times the reference values) and reversible after discontinuation of treatment, but some fatal cases have been reported.

Eye disorders (see section 4.8):
During treatment with amiodarone, regular ophthalmologic examinations including fundoscopy and slit lamp examinations are indicated.
A complete ophthalmologic examination including fundoscopy should be promptly performed in case of blurred or decreased vision. In case of appearance of optic neuropathy and/or optic neuritis, treatment with amiodarone should be stopped due to

the possible progression to blindness.

Serious bullous reactions:
Life - threatening or even fatal cutaneous reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (see section 4.8). If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, amiodarone treatment should be discontinued immediately.

Neuromuscular disorders (see section 4.8):
Amiodarone can cause peripheral neuropathies and / or myopathies. These usually resolve within a few months after discontinuation, but in some cases may not be completely reversible.

Skin:
Exposure to the sun should be avoided during therapy with amiodarone treatment; this also applies to UV light applications and solariums. If this is not possible, the uncovered areas of the skin, especially the face, should be protected with a sun protection ointment with a high sun protection factor. Even after stopping Amiodarone hydrochloride treatment, sun protection is still required for some time.

Pharmacological interactions (see section 4.5):

- Concomitant use of amiodarone with the following drugs is not recommended: beta-blockers, calcium channel inhibitors that decrease heart rate (verapamil, diltiazem), stimulant laxatives that can cause hypokalemia.
- Amiodarone intravenously should only be used in the intensive care unit and under continuous monitoring (ECG, blood pressure).

To avoid reactions at the injection site, amiodarone IV should, whenever possible, be administered by a central venous route (see section 4.8).

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

Recently, cases of hepatotoxicity with amiodarone have been reported after iv administration that could be due to the emulsifier polysorbate 80 (excipient), instead of the medicine itself.

- Pediatric population: the safety and efficacy of amiodarone in pediatric patients has not been established. For this reason, the use of amiodarone is not recommended in these patients.

Amiodarone injection contains benzyl alcohol (20 mg / ml) (see section 2). Benzyl alcohol may cause toxic reactions and anaphylactic reactions in children under 3 years of age.

Cases of fatal "gasping syndrome" have been reported in neonates following intravenous administration of solutions containing this preservative. Symptoms include a sudden onset of gaspings respiration, hypotension, bradycardia and cardiovascular collapse.

The minimum amount of benzyl alcohol at which toxicity may occur is not known.

- Anaesthesia: before surgery, the anaesthetist should be informed that the patient is being treated with amiodarone (see section 4.5).

- Monitoring: during treatment it is necessary to monitor serum potassium levels and transaminases (see section 4.4).

- Electrolyte disorders: hypokalemia can modify the effects of amiodarone and increase the prolongation of the QT interval and the risk of torsades de pointes. The serum potassium deficit should be corrected before starting treatment with amiodarone.

Warning on excipients

This medicine contains 200 mg of benzyl alcohol in each 10ml syringe which is equivalent to 20 mg/ml.

Benzyl alcohol may cause toxic reactions.

In those patients with liver or kidney disease or those who are pregnant or breast-feeding, large amounts of benzyl alcohol should be used with caution and only if necessary, because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction with other medicinal products and other forms of interactions

Drugs inducing "torsades de pointes":
Combined therapy with the drugs which induce "torsades de pointes" is contra-indicated (see section 4.3); for example:

- Class Ia anti-arrhythmic drugs e.g. quinidine, procainamide, disopyramide
- Class III anti-arrhythmic drugs e.g. sotalol, bretylium
- Non antiarryhythmic drugs such as vincamine
- Intravenous erythromycin, co-trimoxazole or pentamidine injection
- Some anti-psychotics e.g. chlorpromazine, levomepromazine, thioridazine, fluphenazine, sulpiride, tiapride, pimozide, haloperidol, amisulpride and sertindole due to the fact that these drugs have an arrhythmogenic effect and/or inhibit CYP3A4 activity and may increase plasma levels of amiodarone.
- Lithium and tricyclic anti-depressants e.g. doxepin, maprotiline, amitriptyline
- Certain antihistamines e.g. terfenadine, astemizole, mizolastine
- Anti-malarials e.g. quinine, mefloquine, chloroquine, halofantrine
- Moxifloxacin
- MAO inhibitors

Drugs that prolong the QT interval
The administration of amiodarone together with drugs that prolong the QT interval should be based on a careful assessment of the risks and benefits for each patient, as the risk of torsades de pointes may be increased. QT interval prolongation should be monitored.

Fluoroquinolones
There have been rare reports of QTc interval prolongation, with or without torsades de points, 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 drugs is not recommended:

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

Drugs causing hypokalaemia
Stimulant laxatives may cause hypokalaemia thus increasing the risk of torsades de pointes; other types of laxatives should be used.

Caution should be exercised over combined therapy with the following drugs which may also cause hypokalaemia and/or hypomagnesaemia: diuretics alone or combined (e.g. hydrochlorothiazide, furosemide), systemic corticosteroids (glucocorticoids, mineralocorticoids), tetracosactide, intravenous amphotericin B.

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 (See section 4.4 and 4.8)
Caution is advised in patients undergoing general anaesthesia, or receiving high dose oxygen therapy.

Potentially severe complications have been reported in patients taking amiodarone while 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. The anaesthesist should be informed that the patient is taking amiodarone.

Effect of amiodarone hydrochloride 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.

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) and conduction may occur. Clinical ECG and biological monitoring is recommended to observe sign 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.

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

Warfarin or Phenprocoumon
The combination of warfarin and phenprocoumon with amiodarone can potentiate the effect of oral anticoagulants and therefore increases the risk of bleeding. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended. The dose of oral anticoagulants (warfarin, phenprocoumon) should be reduced accordingly.

Phenytoin
The combination of phenytoin with amiodarone can lead to an overdose of phenytoin, leading to neurological signs. Phenytoin dosage should be reduced if signs of over dosage (e.g. visual disturbances, tremor, dizziness) appear and plasma levels may be measured.

CYP2D6 substrates
Flecainide
Given that flecainide is mainly metabolized 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.

CYP 3A4 substrates
Amiodarone is an inhibitor of the hepatic microsomal cytochrome 3A4 isoenzyme (CYP 3A4). This inhibition can result in unexpectedly high plasma levels of other drugs which are metabolized by CYP3A4 enzymes.

- 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 (myopathy/rhabdomyolysis) is increased by concomitant administration of amiodarone with statins metabolized by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolized by CYP450 3A4 when given with amiodarone.
- Other drugs metabolized by cytochrome P450 3A4: examples of such drugs are lidocaine, sirolimus, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, macrolide antibiotics (clarithromycin), dihydroergotamine, ergotamine and colchicine.

Interaction with substrates of other CYP 450 isoenzymes
Invitro studies shows that amiodarone also has the potential to inhibit CYP1A2, CYP2C19, CYP2D6 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 hydrochloride
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 should be avoided during treatment with oral amiodarone.

Other drug interactions with amiodarone (see section 4.4)
Coadministration of amiodarone with sofosbuvir containing regimens may lead to serious symptomatic bradycardia.
If coadministration 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-desethylamiodarone 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 an 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 foetus. 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/foetus during early pregnancy.

Amiodarone is contraindicated during pregnancy, except in exceptional circumstances (see section 4.3).

Breast-feeding
Amiodarone and its active metabolite are excreted into the breast milk in significant quantities. Breast-feeding is contraindicated during amiodarone treatment. 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

Amiodarone hydrochloride may affect the ability to drive or use machines. Treatment with this medicine requires regular medical supervision. This medicinal product, even when used as directed, may modify the reaction time to such an extent that the ability to participate actively in road traffic, to operate machinery or to work without a safe grip is impaired. This applies specifically, when starting treatment, increasing the dose and changing the medicinal product, as well as in combination with alcohol.

4.8 Undesirable effects

The presentation of adverse reactions with amiodarone is frequent, particularly cardiac, pulmonary and hepatic toxicity. Sometimes these manifestations are dose related and reversible after a dose reduction.
Adverse reactions are listed in decreasing order of severity within each frequency range.

Frequency of the adverse reaction listed below is defined according to the following convention:

very common (≥1/10);
common (≥1/100 to <1/10);
uncommon (≥1/1,000 to <1/100);
rare (≥ 1/10,000 to <1/1,000);
very rare (<1/10,000);

not known (cannot be estimated from the available data)

Blood and lymphatic system disorders:

- Very rare
- Thrombocytopenia,
- Haemolytic or aplastic anaemi
- Frequency not known:
- Neutropenia,
- Agranulocytosis

Immune system disorders:

- Very rare: anaphylactic shock.
- Frequency not known: angioneurotic oedema (Quincke's Oedema)

Endocrine disorders:

- Common: hyper- and hypothyroidism. Severe hyperthyroidism (in individual cases with fatal outcome), has been reported (see section 4.4)
- Very rare: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Psychiatric disorders:

- Common: libido decreased
- Frequency not known: state of delirium (including state of confusion), hallucination.

Central Nervous system disorders:

- Common:
- Extrapyramidal tremor,
- Nightmares,
- Sleep disturbance
- Uncommon:
- Peripheral sensory neuropathies and/or myopathies, usually reversible after discontinuation of the drug (see section 4.4)
- Dizziness
- Coordination problems
- Paresthesia
- Very rare:
- Benign intra-cranial hypertension (pseudo tumor cerebri)
- Cerebral ataxia
- Headache.

Eye disorders:

- Very common: microdeposits on the anterior surface of the cornea of the eye (can also be called cornea verticillata), which are usually limited to the region below the pupil and can cause visual disturbances (blurred vision, colored halos around light sources). The micro-deposits consist of complex lipid deposits and usually recede 6-12 months after discontinuation of the drug.
- Very rare: optic neuropathy/neuritis that may progress to blindness (see section 4.4).

Cardiac disorders:

- Common: bradycardia, generally moderate.
- Uncommo
- Conduction disturbances (SA block, AV block)
- Episodes of onset or worsening of arrhythmia, sometimes followed by cardiac arrest (see sections 4.4 and 4.5).
- Very rare:
- Severe bradycardia, sinus arrest requiring discontinuation of amiodarone, especially in patients with sinus node dysfunction and/or in elderly patients
- Frequency not known: torsades de pointes (see 4.4 and 5.1). Individual cases of ventricular fibrillation/-flutter have been reported.

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.
- Rare: vasculitis
- Very rare: hot flushes.

Respiratory, thoracic and mediastinal disorders:

- Common
- Hypersensitivity pneumonitis, alveolar pneumonitis, or interstitial pneumonitis or fibrosis, sometimes fatal (see section 4.4)
- Pleurisy, bronchiolitis obliterans organizing pneumonia/BOOP
- Very rare:
- Severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal, usually in the period immediately after surgery; a possible interaction with a high oxygen concentration may be involved (see sections 4.4 and 4.5)
- Bronchospasm and/or apnea in case of severe respiratory failure, and especially in asthmatic patients.

Gastrointestinal disorders:

- Very common:
- Nausea, vomiting
- Taste disturbance at treatment initiation (during administration of loading dose; disappears after dose reduction)
- Uncommon
- Abdominal pain, bloating
- Constipation
- Anorexia
- Frequency not known: pancreatitis /acute pancreatitis

Hepatobiliary disorders:

- Very common
- Isolated and often moderate elevation in serum transaminases (1.5 to 3 times normal range) at the beginning of therapy. They may return to normal with dose reduction or even spontaneously.
- Common:
- Acute liver disorders with high serum transaminases and/or jaundice, including hepatic liver failure, sometimes with fatal outcome (see section 4.4).
- Very rare: chronic liver disease (in individual cases with fatal outcome), liver cirrhosis

Skin and subcutaneous tissue disorders:

- Very common: photosensitization with increased sunburn tendency, which can lead to erythema and skin rash (see section 4.4)
- Common:
- Eczema
- Prolonged treatment with amiodarone (after switch to oral therapy) may result in hyperpigmentation with black-violet to slate gray skin discoloration (pseudocyanosis), especially in the body areas exposed to sunlight. The discolouration will slowly disappear within 1-4 years after discontinuation of the preparation.
- Very rare:
- sweating
- Erythema under radiation therapy
- Erythema nodosum
- Exfoliative dermatitis
- Alopecia
- Frequency not known: Hives, severe skin reactions sometimes fatal including toxic epidermal necrolysis (TEN)/Stevens- Johnson syndrome (SJS), bullous dermatitis and drug reaction with eosinophilia and systemic symptoms (DRESS).

Musculoskeletal and Connective Tissue Disorders

- Common: Muscle weakness
- Frequency not known: Back pain

Renal and urinary disorders:

- Rare: temporarily impaired renal function

Reproductive system and breast disorders

- Very rare:
- Epididymitis
- Erectile dysfunction

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.
- Uncommon: tiredness

Investigations:

- Very rare: increased serum creatinine

Injury, poisoning and complications from surgery:

- Not known: primary graft dysfunction after heart transplantation (see section 4.4).

Other possible side effects:
Hypersensitivity reactions due to benzyl alcohol can rarely occur.

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 HPRA
Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

There is no information available regarding over dosage with intravenous amiodarone.

In cases of acute overdose or too rapid intravenous administration, the following can be observed: nausea, vomiting, constipation, sweating, bradycardia, conduction disturbances and prolonged QT interval. Following substantial overdose, onset of hypotension, heart block and torsades de pointes should also be expected. In exceptional cases, hyperthyroidism may occur.

Following substantial overdose, prolonged ECG monitoring must be performed. Intensive care unit admission should be considered. Hypotension can be treated with infusion fluids or vasopressors. The use of alpha- or beta adrenergic agents or temporary pacing may be indicated. Class Ia and III antiarrhythmic agents should be avoided, as they are associated with QT interval prolongation and induction of torsades de pointes. Further treatment should be supportive and symptomatic. 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.Cases of circulatory failure and hepatic failure have been reported. Bradycardia caused by amiodarone injection is atropine resistant.

Due to the pharmacokinetics of amiodarone, adequate and prolonged surveillance of the patient, particularly their cardiac status, is recommended. Neither amiodarone nor its metabolites are dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: -Cardiac therapy, antiarrhythmics, class III

ATC code: - C01B D01

Mechanism of action:
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, IKr). Thus, it prolongs the refractory period of the action potential leading to depression of ectopies and re-entry-arrhythmias and to prolongation of the QTc interval in the ECG. Furthermore, amiodarone also blocks cardiac Na+ currents (class I effect) and Ca2+ 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.

Pharmacodynamic effects:
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.

Clinical efficacy and safety:

The safety and efficacy of amiodarone IV in patients with out-of-hospital cardiac arrest as a result of shock-resistant ventricular fibrillation have been evaluated in two double-blind studies: the ARREST study, which compared amiodarone with placebo, and the ALIVE study, which compared amiodarone with lidocaine. The primary endpoint of both studies was the number of patients who survived until hospital admission.

In the ARREST study, 504 patients – with out-of-hospital cardiac arrest as a result of ventricular fibrillation, or pulseless ventricular tachycardia refractory to 3 or more defibrillator shocks and epinephrine – were given either 300 mg amiodarone diluted in 20 ml 5% glucose as a rapid injection into a peripheral vein (246 patients) or placebo (258 patients). Of the 197 patients (39%) who survived the journey to hospital, amiodarone significantly increased the chances of resuscitation and hospital admission: 44% in the group receiving amiodarone versus 34% in the group treated with placebo (p = 0.03). After adjustment for other independent predictors, the adjusted ratio for survival to hospital admission was 1.6 (95% confidence interval, 1.1 to 2.4; p = 0.02) in the group receiving amiodarone, compared with the placebo group. Incidence of hypotension (59% versus 25%, p = 0.04) and bradycardia (41% versus 25%, p = 0.004) was more common in patients receiving amiodarone than in patients receiving placebo.

In the ALIVE study, 347 patients – with ventricular fibrillation resistant to three defibrillation shocks, intravenous epinephrine and a further defibrillation shock, or with recurrenceof ventricular fibrillation after initially successful defibrillation, were randomized to rapidly receive through peripheral venous administration amiodarone (5 mg/kg of estimated bodyweight diluted in 30 mL 5% glucose) andlidocaine matching placebo, or lidocaine (1.5 mg/kg at a concentration of 10 mg/mL)and amiodarone-matching placebo containing the same diluent (polysorbate 80). Amiodarone significantly increased the chances to be resuscitated and admitted to the hospital: of the 347 patients enrolled, 22.8% in the amiodarone group (41 patients out of 180) survived to hospital admission, vs 12% in the lidocaine group (20 patients out of 167), p = 0.009. After adjustment for other factors that may influence the likelihood of survival, the adjusted odds ratio for survival to hospital admission was 2.49 (95% confidence interval, 1.28 to 4.85; p = 0.007).There were no differences between the amiodarone and lidocaine groups in the proportions of patients who needed treatment of bradycardia with atropine or vasopressor treatment with dopamine, or in the proportions of patients receiving open-label lidocaine. 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.

Intravenous administration

Absorption:
After injection the maximal effect is reached after 15 minutes.

Distribution:
After this time, there is distribution into the tissue and a fast decrease of the plasma level within 4 hours.

To achieve saturation of the tissue treatment needs to be continued intravenously or orally. During saturation, amiodarone is accumulated particularly in the fat tissue and steady state is reached within a period of one to several months.

Because of these characteristics, the recommended saturating dosage should be given in order to reach fast saturation of the tissue which is the prerequisite for therapeutic efficacy. 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 using a two-compartment open model are similar for both groups. Elimination of amiodarone after intravenous injection appeared to be biexponential with a distribution phase lasting about 4 hours. The very high volume of distribution combined with a relatively low apparent volume for the central compartment suggests extensive tissue distribution.

The mean values of distribution of amiodarone after a single dose of amiodarone i.v. (5 mg/kg in 15 minutes) are as follows: volume of central distribution 0.2 L/kg and in stationary phase: 40-84 L/kg. For its active metabolite the volume of distribution in stationary phase: 68-168 L/kg.)

Biotransformation:
Amiodarone is metabolized primarily through CYP 3A4 and also through CYP P2C8. Amiodarone and its metabolite, desethylamiodarone, show an in vitro potential to inhibit CYP 1A1, CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, CYP 3A4, CYP 2A6, CYP 2B6 and 2C8. Amiodarone and desethylamiodarone also have the potential to inhibit some transporters such as Gp-P and the organic cation transporter (OCT2). (One study shows a 1.1% increase in the concentration of creatinine,a substrate of OCT2). In vivo data describes interactions with CYP 3A4, CYP2C9, CYP 2D6 and Gp-P substrates.

The main active metabolite of amiodarone in humans is desethylamiodarone (DEA). It is thought that the enzyme responsible for the desethylation is cytochrome P450 3A4.

Elimination:
Amiodarone hydrochloride has a long half-life which varies interindividually between 20 and 100 days.

The main elimination route is via the liver and the bile. 10 % of the substance is eliminated renally.

Due to the low renal elimination the usual dosage can be administered to patients with renal insufficiency.

After discontinuation amiodarone is excreted over several months.

The mean values of elimination of amiodarone after a single dose of amiodarone iv (5 mg/kg in 15 minutes) are as follows: clearance: 90-158 mL/h/kg and $t_{½}$: 20-47 days. For its active metabolite the clearance: 197-290 mL/h/kg and $t_{½}$ =$t_{½}$ of amiodarone.

A study in both healthy volunteers and patients after intravenous administration of amiodarone reported that the calculated total blood clearance using a two-compartment open model were similar for both groups. Elimination of amiodarone after intravenous injection appeared to be biexponential. A bolus IV injection of 400mg gave a terminal T½ of approximately 11 hours.

Age, sex, alterations in renal or hepatic function do not have marked effects on the disposition of amiodarone or its active metabolite.

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 repeat dose 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, dogs, pigs and baboons. Amiodarone had indirect effects on serum lipids with changes in plasma concentrations of thyroid hormones.

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.

Amiodarone hydrochloride is a highly phototoxic substance. There is evidence that cytotoxic free radicals are formed in the presence of amiodarone hydrochloride by UV irradiation. This cannot only lead to acute phototoxic reactions, but also to DNA damage (photomutagenicity) and subsequent photocarcinogenic effects. Until now, these potentially serious side effects of amiodarone hydrochloride have not been investigated experimentally. Therefore, the photomutagenic and photocarcinogenic potential of amiodarone is not known.

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

In reproduction toxicity studies, in rats, amiodarone has shown potential adverse effects on fertility and postnatal development. Amiodarone was embryotoxic but not teratogenic in rats and rabbits at clinically relevant doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Polysorbate 80
Water for Injections

6.2 Incompatibilities

Amiodarone is incompatible with saline solution.

The use of administration equipment or devices containing plasticizers such as DEHP (di-2-ethylhexyphthalate) 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.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

After dilution, chemical and physical in-use stability has been demonstrated for 3 hours, 48 hours and 15 minutes at concentration 1.2 mg/ml, 2.4 mg/ml & 15 mg/ml respectively at 20-25 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of user.

6.4 Special precautions for storage

Do not store above 25 °C. Keep the syringe in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

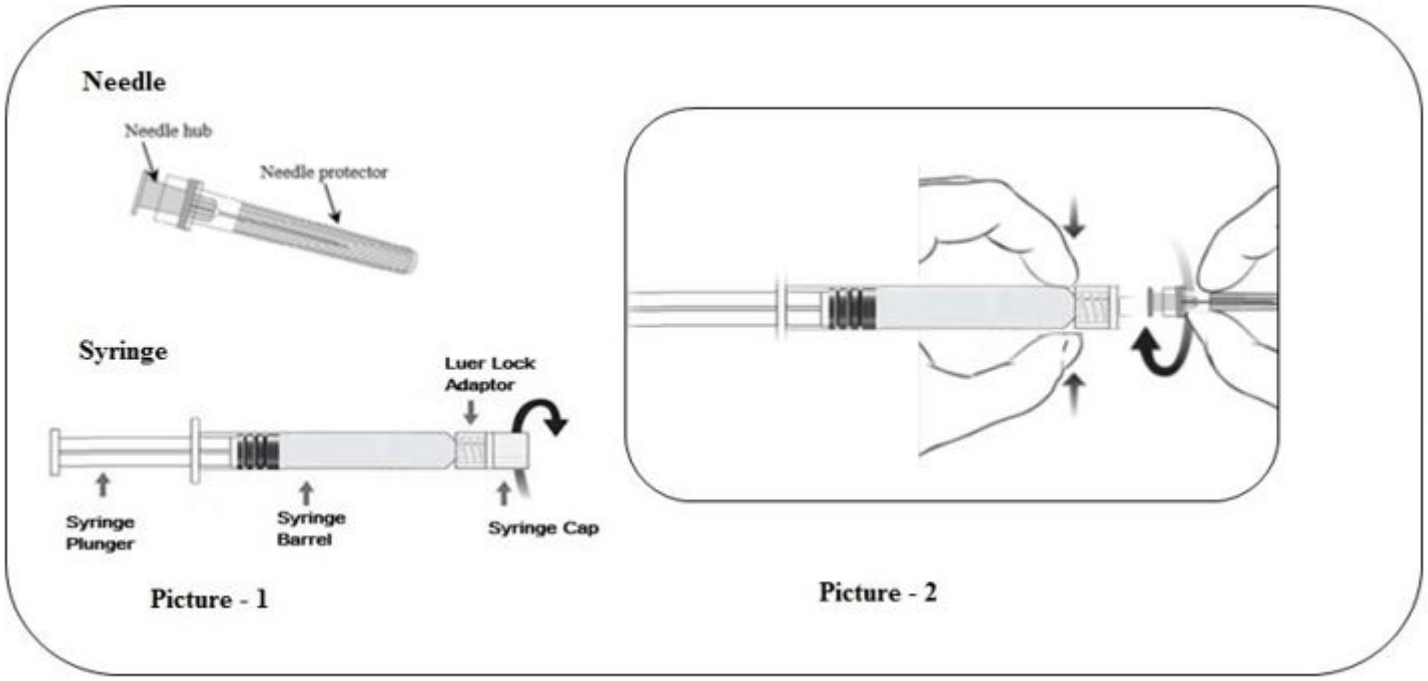
6.5 Nature and contents of container

10 ml Type-I clear glass syringe with bromobutyl plunger stopper and polypropylene plunger rod.

Glass syringe has graduation mark per mL up to 10 mL.
Pack size: 1 syringe

6.6 Special precautions for disposal and other handling

Before use, the sterile concentrate should be visually inspected for clarity, particulate matter and the integrity of the container. The solution should only be used if it is clear colorless to pale yellow solution and the container is undamaged and intact. Prior to administration by intravenous infusion, Amiodarone hydrochloride 30 mg/ml concentrate for solution for injection/infusion in syringe should be diluted according to directions with 5% dextrose. One syringe of Amiodarone hydrochloride 30 mg/ml concentrate for solution for injection/infusion diluted as recommended in 500 ml of 5% dextrose results in a concentration of 0.6 mg/ml of amiodarone hydrochloride. On account of the stability of the solution, do not use concentrations below 0.6 mg/ml and do not add other medicinal products to the infusion fluid.
Instructions for handling and administration



- Unscrew the glass syringe cap by twisting it anticlockwise (as illustrated in picture -1).
- Attach the needle to the syringe by gently connecting the needle hub into the luer lock adapter and rotate a quarter turn clockwise until you feel it lock (as illustrated in picture -2).
- Carefully remove the needle cap by pulling it straight off.
- **Dilute further** (see section 4.2) with dextrose 5% as per instructions **for intravenous injection**

Prior to administration by **intravenous infusion**, Amiodarone hydrochloride 30 mg/ml concentrate for solution for injection/infusion in syringe **must be diluted** according to directions with 5% dextrose. One syringe of Amiodarone hydrochloride 30 mg/ml concentrate for solution for injection/infusion diluted as recommended in 500 ml of 5% dextrose results in a concentration of 0.6 mg/ml of amiodarone hydrochloride. On account of the stability of the solution, do not use concentrations below 0.6 mg/ml and do not add other medicinal products to the infusion fluid.

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

For single use only.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857

Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/210/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th September 2021

10 DATE OF REVISION OF THE TEXT

May 2022