SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amiodarone Hydrochloride 20 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 20 mg amiodarone hydrochloride, equivalent to 18.9 mg amiodarone.

Each vial with 50 ml of solution contains 1000 mg amiodarone hydrochloride, equivalent to 946.54 mg amiodarone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

Clear, slightly green-yellow solution free from visible particles.

pH 2.8 – 3.6

Osmolality 270-310 mOsmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amiodarone hydrochloride is indicated for the treatment of serious cardiac arrhythmias in adults, in cases where other therapies are not effective or contraindicated:

- atrial arrhythmias, including paroxysmal atrial fibrillation or flutter
- AV nodal arrhythmias and AV reentrant tachycardia, e.g. as a manifestation of Wolff-Parkinson-White syndrome
- life-threatening ventricular arrhythmias, including persistent or non-persistent ventricular tachycardia or episodes of ventricular fibrillation

Amiodarone Hydrochloride 20 mg/ml solution for infusion can be used where a rapid response is required or where oral administration is not possible.

Amiodarone hydrochloride may be used prior to DC cardioversion.

4.2 Posology and method of administration

Treatment should be initiated and normally monitored only under hospital or specialist supervision when facilities for cardiac monitoring, defibrillation, and cardiac pacing are available. Amiodarone Hydrochloride 20 mg/ml solution for infusion should be administered by health care professionals who are experienced in the treatment of serious cardiac arrhythmias and are thoroughly familiar with the risks and benefits of the use of amiodarone via intravenous routes.

Thyroid function test should be performed where appropriate prior to therapy in all patients.

Protecting skin from sunlight is required during therapy as patients receiving amiodarone can become unduly sensitive to sunlight, which may persist after several months of discontinuation of therapy.

Posology
Adults

Loading infusion:
Administer 5 mg per kg body weight over 20 minutes to 2 hours (see Table 1) and repeat 2 - 3 times every 24 hours up to 1200 mg (approximately 15 mg/kg body weight) per 24 hours, the rate of infusion being adjusted on the basis of clinical response (see section 4.4).

Table 1 Recommended initial loading doses of amiodarone hydrochloride at 5 mg per kg of body weight and corresponding infusion rates.

Patient's weight (kg)	Amiodarone HCl dose (mg)	Volume (ml) of 20 mg/ml solution for infusion	Infusion rate over **20 minutes** (ml/minute)	Infusion rate over 2 **hours** (ml/hour)
50	250	12.50	0.625	6.25
55	275	13.75	0.688	6.875
60	300	15.00	0.750	7.5
65	325	16.25	0.813	8.125
70	350	17.50	0.875	8.75
75	375	18.75	0.938	9.375
80	400	20	1	10
85	425	21.25	1.063	10.625
90	450	22.5	1.125	11.25

95	475	23.75	1.188	11.875
100	500	25	1.25	12.5

The effect occurs within a few minutes and decreases gradually. Therefore, it must be followed by a maintenance infusion.

Maintenance infusion:
Administer 10 - 20 mg per kg body weight every 24 hours (on average 600 to 800 mg/ 24 hours up to a maximum of 1200 mg/ 24 hours) for a few days (see Table 2).

Table 2 Recommended maintenance dose of amiodarone hydrochloride.

Amiodarone HCl dose (mg)	Volume (ml) of 20 mg/ml solution for infusion	Infusion rate over **24 hours** (ml/hour)
600	30	1.25 [= 0.02ml/ min]
800	40	1.67 [= 0.03ml/ min]
1200	60	2.50 [= 0.04ml/ min]

Changeover from intravenous to oral therapy:
Amiodarone Hydrochloride 20 mg/ml solution for infusion is normally administered only to initiate therapy, for no longer than one week. As soon as an adequate response has been obtained, oral therapy should be initiated concomitantly at the usual loading dose (i.e. 200 mg three times a day). Amiodarone hydrochloride should then be phased out gradually.

Paediatric population
The safety and efficacy of amiodarone in neonates, children and adolescents has not been established. Currently available data are described in sections 5.1 and 5.2.

Elderly patients
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
Intravenous infusion only.

Amiodarone Hydrochloride 20 mg/ml solution for infusion must be administered only as an undiluted intravenous infusion using a controlled infusion device (e.g. syringe driver/syringe pump) capable of accurately and consistently delivering the specified volume at a strictly controlled rate of infusion.

Amiodarone Hydrochloride 20 mg/ml solution for infusion should not be diluted before use; it is supplied ready to use. Inadvertent dilution of Amiodarone Hydrochloride 20 mg/ml solution for infusion could lead to under-dosing of the patients and decreased therapeutic response.

Amiodarone Hydrochloride 20 mg/ml solution for infusion must not be administered as a direct IV (bolus) injection.

Intravenous amiodarone concentrations exceeding 2 mg/ml, such as Amiodarone Hydrochloride 20 mg/ml solution for infusion, containing 20 mg/ml, are associated with peripheral vein irritation/phlebitis. Amiodarone Hydrochloride 20 mg/ml solution for infusion must be administered via a central line, especially if repeated or continuous infusions are required (see section 4.4).

Amiodarone Hydrochloride 20 mg/ml solution for infusion should not be mixed with other medicines (see section 6.2) and is incompatible with sodium chloride 0.9% infusion fluids.

In situations where it may be urgently required to administer concomitant medicinal products through a central line, careful consideration should be given to the compatibility of the medicinal products administered and the type of vascular access device used.

During maintenance infusion, the product should be protected from light.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.;
- Severe respiratory failure, circulatory collapse, or severe arterial hypotension;
- Evidence or history of thyroid dysfunction (see section 4.2 and 4.4);
- Sinus bradycardia, sino-atrial heart block and sick sinus syndrome in patients without a pacemaker. 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;
- Concomitant use of medicinal products which may induce torsade de pointes arrhythmia (see section 4.5);
- Iodine allergy (one vial contains approximately 372 mg iodine);
- Pregnancy and lactation. The use is allowed only in special life-threatening circumstances as specified in sections 4.1, 4.4 and 4.6;

- Cardiopulmonary resuscitation of ventricular fibrillation /pulseless ventricular tachycardia resistant to defibrillation as Amiodarone Hydrochloride 20 mg/ml solution for infusion is not intended for direct (bolus) IV injection.

4.4 Special warnings and precautions for use

Primary Graft Dysfunction post cardiac transplant
In retrospective studies, amiodarone use in the transplant recipient prior to heart transplant has been associated with an increased risk of primary graft dysfunction (PGD). PGD is a life-threatening complication of heart transplantation that presents as left, right or biventricular dysfunction occurring within the first 24 hours of transplant surgery for which there is no identifiable secondary cause (see 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.

Amiodarone Hydrochloride 20 mg/ml solution for infusion contains polysorbate 80 (see section 2)
Polysorbates may cause hypotension and heart rate changes (potential cardiotoxicity). The risk of severe hypotension can be minimised by slowing down the infusion. Electrophysiological studies show cardiac depression in dogs and inhibition of hERG currents by polysorbates *in vitro*. The potential for torsade de pointes in humans is unknown.

Rarely, polysorbates can cause severe allergic reactions including symptoms such as dyspnoea, swelling and dizziness (see section 4.8).

Cases of hepatotoxicity (abrupt elevation of liver enzymes) linked to exposure to polysorbates after IV administration of amiodarone were reported therefore cumulative daily doses of polysorbate 80 should not exceed 35 mg/kg (corresponding to 17.5 mg amiodarone hydrochloride/kg or 0.875 ml of solution for infusion/kg) in adults and children. However, it needs to be taken into consideration that amiodarone itself can cause hepatotoxicity.

Administration
Amiodarone hydrochloride should only be used in a special care unit under continuous monitoring (ECG and blood pressure) where facilities for cardiac pacing and defibrillation exist.

Circulatory collapse may be precipitated by too rapid administration or overdosage.

Intravenous amiodarone concentrations exceeding 2 mg/ml, such as Amiodarone Hydrochloride 20 mg/ml solution for infusion ,containing 20 mg/ml, are associated with peripheral vein irritation/phlebitis.

Amiodarone Hydrochloride must be administered via a central line.

Monitoring
Cardiac function (ECG) monitoring should be facilitated and serum potassium levels, liver, thyroid, lung function tests, and chest x-ray should be performed before

initiating of treatment. Liver enzymes should be checked at regular intervals during treatment.

Careful monitoring for signs of extravasation (following local guidelines) of the Central Venous Access Device and the surrounding area, should be undertaken both during and following an infusion.

Prolonged phototoxicity
Because of the possibility of phototoxic reaction, sunlight exposure should be avoided during and after discontinuation of therapy with amiodarone; this also applies to UV light and solariums/sunbeds. If this cannot be avoided, the uncovered skin areas, especially the face, should be protected by topical preparations with a high sun protection factor. Even after discontinuation of Amiodarone Hydrochloride 20 mg/ml solution for infusion, sun protection is still required for several months due to extensive distribution and long half-life of amiodarone in the body.

Cardiac disorders
In patients with hypotension and decompensated cardiomyopathy and severe heart failure caution should be exercised and hemodynamic monitoring should be facilitated (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 cardiac glycoside therapy. In these circumstances, amiodarone hydrochloride 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. Excessive QT prolongation may increase the risk of torsade de pointes arrhythmia, therefore patients with pre-existing QT prolongation should be carefully monitored.

Severe bradycardia and heart block
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 Hepatitis C Virus (HCV) treatment.

Amiodarone should only be used in patients on a 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 a sofosbuvir- containing regimen.

All patients receiving amiodarone in combination with a 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.

General anaesthesia
Before surgery, the anaesthetist should be informed that the patient is receiving amiodarone.
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 (see section 4.5).

Endocrine disorders (see section 4.8)
Due to the risk of developing a thyroid dysfunction (hyper- or hypothyroidism) under treatment with Amiodarone Hydrochloride 20 mg/ml solution for infusion, thyroid function tests should be carried out before initiating treatment.
During therapy and up to one year after discontinuation of therapy, these examinations should be repeated at regular intervals and patients should be examined for clinical signs of hyper- or hypothyroidism.

Amiodarone may induce hyperthyroidism, particularly in patients with a personal history of thyroid disorders or patients who are taking/have previously taken oral amiodarone. The following, usually mild symptoms should alert the physician: weight loss, tachycardia, tremor, nervousness, increased sweating and heat intolerance, recurrence of arrhythmia or angina pectoris, heart failure.
Serum ultrasensitive **thyroid-stimulating hormone** (usTSH) level should be measured when thyroid dysfunction is suspected. Thyroid function tests should be performed where appropriate prior to therapy in all patients.
The clinical diagnosis of hyperthyroidism is confirmed by evidence of significantly reduced usTSH and increased T_3 and T_4 levels. If hyperthyroidism is detected, Amiodarone Hydrochloride 20 mg/ml solution for infusion should be discontinued. Improvement occurs within a few months after discontinuation and is accompanied by normalisation of thyroid function tests. In severe cases (sometimes fatal), individual emergency treatment with thyrostatic medications, beta-blockers and/or corticosteroids must be initiated.

The following symptoms may be indications of hypothyroidism: Weight gain, sensitivity to cold, fatigue, extreme bradycardia beyond the effect expected with Amiodarone Hydrochloride 20 mg/ml solution for infusion. The clinical diagnosis of hypothyroidism is confirmed by evidence of significantly increased usTSH and decreased T4. Euthyroidism usually develops within 1-3 months after discontinuation of treatment. If hypothyroidism is detected, the amiodarone dose should be reduced if possible and/or substitution with levothyroxine should be started. In individual cases, discontinuation of Amiodarone Hydrochloride 20 mg/ml solution for infusion may be necessary.

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 thyroxine (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.

Respiratory, thoracic and mediastinal disorders (see section 4.8)
Under treatment with Amiodarone Hydrochloride 20 mg/ml solution for infusion there is a risk of developing severe inflammatory lung diseases (hypersensitivity pneumonitis, alveolar or interstitial pneumonitis). Onset of dyspnoea or non-productive cough may be signs of these pulmonary alterations. In addition, weight loss, fever and weakness may occur.

Therefore, a chest X-ray and lung function test should be performed before starting treatment. During the further course of treatment, these examinations should be repeated at intervals of about 3-6 months.
These examinations should also be carried out if breathing difficulties occur (symptom of possible lung toxicity). In patients with severe lung diseases, lung function may have to be checked more frequently, as these patients have a worse prognosis if lung toxic effects occur.

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 alveolar/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 hydrochloride. 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)
Rare cases of hepatocellular necrosis, leading to death have been linked to intravenous infusions of amiodarone at higher concentrations and infusion rates much faster than recommended (see section 4.8). Therefore, patients receiving IV amiodarone should be carefully monitored for evidence of progressive hepatic injury. In such cases the rate of administration should be reduced or amiodarone hydrochloride therapy should be withdrawn. Close monitoring of liver function tests (transaminases) is necessary as soon as amiodarone is started and at regular intervals during treatment. At the start of the treatment a mild to moderate increase (1.5 to 3 times normal) of transaminases may occur. This increase is often transient in nature and resolves spontaneously upon lowering the dose.
Acute hepatic impairment (including severe hepatocellular insufficiency or hepatic failure, sometimes fatal) and chronic liver disorders may occur in both oral and intravenous administration of amiodarone, and within the first 24 hours after intravenous administration. Therefore, amiodaron dosage should be reduced or the treatment discontinued if transaminase increase exceeds three times the normal range. Clinical and biological signs of chronic liver disorders with oral administration of

amiodarone may be minimal (hepatomegaly, transaminase increase up to 5 times the normal value) and reversible after the treatment withdrawal. However, cases with fatal outcome have been described.

Intravenous exposure to polysorbate 80, which is used as excipient, may also cause abrupt elevation of liver enzymes and hepatotoxicity (see section 2).

Severe bullous reactions
Life-threatening or even fatal cutaneous reactions such as Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) have been reported (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 diseases (see section 4.8)
Amiodarone may cause peripheral neuropathies and/or myopathies. They usually disappear a few months after discontinuation, but may not be fully reversible in rare cases.

Eye disorders (see section 4.8)
During treatment with amiodarone, regular ophthalmological examinations, including funduscopy and slit lamp examinations, are recommended. 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.

Drug interactions (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.

In cases of hypokalaemia, corrective action should be taken and QT interval monitored. In case of torsade de pointes antiarrhythmic agents should not be given; pacing may be instituted and IV magnesium may be used.

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.

Amiodarone is an inhibitor of the cytochrome P450 enzyme CYP3A4. Therefore, statins that are metabolised via CYP3A4 (e.g. simvastatin, atorvastatin, lovastatin) should not be used simultaneously with amiodarone.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs that may induce torsade de pointes arrhythmia
Combined therapy with the following drugs that may cause torsade de pointes arrhythmia are contraindicated (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;
- intravenous erythromycin, co-trimoxazole or pentamidine injection;
- MAO inhibitors e.g. moclobemide;
- some anti-psychotics e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride, sulpiride, and sertindole;
- lithium and tricyclic anti-depressants e.g. doxepin, maprotiline, amitriptyline;
- certain antihistamines e.g. terfenadine, astemizole, mizolastine;
- anti-malarials e.g. quinine, mefloquine, chloroquine, halofantrine;
- moxifloxacin;
- cisapride.

Drugs that prolong the QT interval
Concomitant use of amiodarone and medicinal products known to prolong the QT interval must be based on a careful assessment of the possible risks and benefits for each patient, as the risk of torsade de pointes may increase. Patients should be monitored for QT prolongation

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 drugs is not recommended:

- Beta blockers and certain calcium channel inhibitors (diltiazem, verapamil); potentiation of negative chronotropic properties and conduction slowing effects may occur;
- Stimulant laxatives, which may cause hypokalaemia thus increasing the risk of torsade de pointes; other types of laxatives should be used.

Combined therapy with the following drugs which may also cause hypokalaemia and/or hypomagnesaemia should be considered with caution:

- diuretics;
- systemic corticosteroids;
- tetracosactide;
- intravenous amphotericin B.

General anaesthesia
Potentially severe complications such as bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output have been reported in patients taking amiodarone undergoing general anesthesia (see section 4.4).

Very rare cases of severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal, have been observed usually in the period immediately following surgery. A possible interaction with a high oxygen concentration may be implicated (see section 4.4).

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 hydrochloride 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 cardiac glycoside toxicity and digoxin dosage should be halved.

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) and phenytoin by inhibition of the cytochrome P450 2C9.

Warfarin
The dose of warfarin should be reduced accordingly. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended.

Phenytoin
Phenytoin dosage should be reduced if signs of overdosage (e.g. impaired vision, tremor, dizziness) appear, and plasma levels may be measured.

CYP2D6 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.

CYP P450 3A4 substrates
When drugs 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 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, sirolimus, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine, ergotamine and colchicine.

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 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 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)
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-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 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.

Breast-feeding

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. The use is allowed only in special life-threatening circumstances as specified in sections 4.1, 4.3 and 4.4.

Fertility

Elevated serum levels of Luteinizing hormone (LH) and Follicle-stimulating hormone (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.

4.8 Undesirable effects

The most common adverse drug effects reported with intravenous amiodarone hydrochloride are infusion phlebitis, bradycardia, and hypotension.

Table 1: Frequency of the adverse reaction

System Organ Class	**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					Haemolytic or aplastic anaemia	-In patients taking amiodarone there have been incidental findings of bone marrow granulomas. The clinical significance of this is unknown. -Neutropenia - Agranulocytosis
Immune system disorders					Anaphylactic shock	Angioedema
Endocrine disorders		-Hyperthyroidism, sometimes fatal (see section 4.4) -Hypothyroidism			Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	-
Psychiatric disorders		Libido decreased				-Delirium (including confusion) - Hallucination
Reproductive system and breast disorders					Epididymitis	Sexual dysfunction
Nervous system disorders		-Extrapyramidal tremor -Nightmares -Sleep disturbances	-Peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the drug -Dizziness -Impaired coordination -Paresthesia		- Benign intracranial hypertension (pseudo-tumour cerebri) - Cerebral ataxia - Headache	
Eye disorders	Microdeposits at the anterior surface of the cornea are found in almost every patient, which are usually limited to the area below the pupil. They				Optic neuropathy/neuritis that may progress to blindness.	

System Organ Class	**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)
	may be associated with colored halos in dazzling light or blurred vision. They usually regress 6-12 months after discontinuation of amiodarone hydrochloride.					
Cardiac disorders		- Dose-dependent bradycardia	- Conduction disturbances (sinoatrial block, AV block); in individual cases the occurrence of asystole was observed. - Occurrence of new - and exacerbation of existing arrhythmias, sometimes followed by cardiac arrest (see also section 4.4 and 4.5)		Severe bradycardia (in cases of sinus node dysfunction and in the elderly) or (more rarely) sinus arrest: this may necessitate discontinuation of the treatment. -	- Torsade de pointes (see also section 4.4 and 4.5) - Isolated cases of ventricular fibrillation/ flutter have been described.
Vascular disorders		- Hypotension and increased heart rate immediately following injection. These are generally moderate and transient in nature. Cases of severe hypotension or shock have been reported following overdose or		Vasculitis	Hot Flushes	

System Organ Class	**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)
		too rapid administration (bolus injection).				
Respiratory, thoracic and mediastinal disorders		- Hypersensitivity pneumonitis - Alveolar/interstitial pneumonitis or fibrosis - Pleuritis - Bronchiolitis obliterans organizing pneumonia (BOOP) - Individual fatal cases were reported (section 4.4).			- Acute adult respiratory distress syndrome (mostly after surgery), sometimes with fatal sequelae - Bronchospasm and/or apnoea in patients with serious respiratory problems, especially patients with asthma	
Gastrointestinal disorders	-Nausea -Vomiting -Taste disturbances at treatment initiation (disappear after dose reduction)	-	- Abdominal pain - Bloating - Constipation - Anorexia			Pancreatitis (acute)
Hepatobiliary disorders	A mild to moderate increase in transaminase levels (1.5 to 3 times above normal) at the start of treatment, which is often transient in nature and resolves spontaneously upon lowering the dose	Acute liver function disorders, with increased serum transaminase and/or jaundice, including hepatic failure, sometimes with fatal sequelae (see section 4.4)			- Chronic liver disease (sometimes fatal) - Liver cirrhosis	
Skin and subcutaneous tissue disorders	Photosensitization with increased sunburn tendency, which can lead to erythema	Eczema			-Erythema formation under radiation therapy -Erythema nodosum	- Urticaria - Severe skin reaction as toxic epidermal necrolysis (TEN)/Stevens-Johnson

System Organ Class	**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)
	and skin rash (see section 4.4).				-Exanthema -Exfoliative dermatitis -Alopecia -Sweating	syndrome (SJS), bullous dermatitis and Drug reaction with eosinophilia and systematic symptoms (DRESS)
Musculoskeletal and Connective Tissue Disorders		Muscle weakness				Back pain
General disorders and administration site conditions		At the site of injection or infusion: pain, erythema, oedema, necrosis, extravasation, infiltration, inflammation, induration, thrombophlebitis, phlebitis, cellulitis, infection, pigmentation changes	Fatigue	The excipient polysorbate 80 may cause allergic reactions.		
Renal and urinary disorders						Rise in serum creatinine levels
Injury, poisoning and procedural complications						Primary graft dysfunction post cardiac transplant (see section 4.4)

Rarely, polysorbates can cause severe allergic reactions (dyspnoea, swelling, dizziness), and hepatotoxicity (abrupt elevation of liver enzymes). Polysorbates can also have cardiovascular effects (e.g. hypotension, cardiac depression).

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 national reporting system listed in Appendix V.

4.9 Overdose

There is no information regarding overdosage with intravenous amiodarone.

In cases of acute overdose or too rapid intravenous administration, the following can be observed: nausea, vomiting, constipation, sweating, bradycardia, prolonged QT interval, spontaneously ceasing tachycardia, circulatory collapse, hepatic failure. Following substantial overdose, onset of hypotension, heart block and torsade 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 bradycardia caused by Amiodarone Hydrochloride 20 mg/ml solution for infusion is resistant to atropine. 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 torsade de pointes. Further treatment should be supportive and symptomatic.

Amiodarone and its metabolites cannot be dialysed.

Due to the pharmacokinetics of amiodarone, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, antiarrhythmics, class III
ATC code: C01BD01

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 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.

Pharmacodynamic effects
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.

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

Intravenous administration
Absorption
Following IV infusion absorption is expected to be 100%. 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.

The accumulation of amiodarone in the myocardial tissue is required for its therapeutic efficacy. Depending on the saturation dosage the therapeutic effects can be expected between a few days and up to two weeks. 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.

Biotransformation
Amiodarone is mainly metabolised via CYP3A4 and also via CYP2C8. Amiodarone and its metabolite, desethylamiodarone, show *in vitro* the potential to inhibit CYP1A1, CYP1A2, CYP2C9, CYP2D6, CYP3A4, CYP2A6, CYP2B6 and CYP2C8. Amiodarone and desethylamiodarone also have the potential to inhibit some transporters, such as P-glycoprotein and organic cation transporters (OCT2) (one study shows a 1.1% increase in the concentration of creatinine, an OCT2 substrate). *In vivo* data describe an interaction of amiodarone and CYP3A4, CYP2C9, CYP2D6 and P-gp substrates.

Elimination
Amiodarone has a slow elimination rate and a marked affinity for tissue. 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.

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 hydrochloride caused similar toxic effects in animals as in humans. Amiodarone led to pulmonary damage (fibrosis, phospholipidosis; in hamsters, rats and dogs) as well as CNS disorders (in rats). 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. 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 can lead not only to acute

phototoxic reactions, but also to damage to DNA (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 epigenetic 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

Glucose monohydrate
Hydrochloric acid (for pH adjustment)
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

In the presence of amiodarone the use of administration equipment containing softening agents such as DEHP (di-2-ethylhexyl phthalate) may cause DEHP to leach into the solution. In order to minimise patient exposure to DEHP, amiodarone solutions for infusion should be administered through sets that do not contain DEHP, such as polyolefin (PE, PP) or glass sets. No other agents may be added to amiodarone infusions.

6.3 Shelf life

Unopened vial: 2 years.

In-use shelf life:
The medicinal product should be used immediately after first opening.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

50 ml solution for infusion in 50 ml clear, type II glass vial, closed with bromobutyl rubber stopper and tear-off top cap.
Pack sizes:
1, 5, 10 x 50 ml vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Amiodarone Hydrochloride 20 mg/ml solution for infusion is already diluted and ready to use. It should be used without prior dilution. It should be used with a suitable syringe driver/syringe pump capable of accurately and consistently delivering the specified volume at a strictly controlled rate of infusion.

Before use, the solution for infusion 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 and the container is undamaged and intact.

Do not add other medicinal products to the infusion fluid (see section 6.2).

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

During maintenance infusion, the product should be protected from light.

7 MARKETING AUTHORISATION HOLDER

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Nexus, Gloucester Business Park
Gloucester, GL3 4AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 01502/0113

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/04/2025

10 DATE OF REVISION OF THE TEXT

14/01/2025