SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion contains 50 mg amiodarone hydrochloride equivalent to 46.9 mg amiodarone.

Each ampoule with 3 ml of Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion contains 150 mg amiodarone hydrochloride.

One ampoule of Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion diluted as recommended in 250 ml of glucose 5% results in a concentration of 0.6 mg/ml of amiodarone hydrochloride.

Excipient with known effect:

1 ml Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion contains 22.2 mg of benzyl alcohol.

Each ampoule with 3 ml contains 66.6 mg of benzyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for Solution for Injection and Infusion.

Clear pale yellow sterile solution.

pH 3.5-4.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- atrial arrhythmias, including 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 50 mg/ml Concentrate for Solution for Injection/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.

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

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

Posology

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 glucose 5%. This may be followed by repeat infusion up to 1200mg (approximately 15mg/kg bodyweight) in up to 500ml glucose 5% per 24 hours, the rate of infusion being adjusted on the basis of clinical response (see section 4.4).

In extreme clinical emergency the drug may, at the discretion of the clinician, be given as a slow intravenous injection of 150-300mg in 10-20ml glucose 5% over a minimum of 3 minutes. This should not be repeated for at least 15 minutes. Patients treated in this way with amiodarone hydrochloride must be closely monitored, e.g. in an intensive care unit (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 (i.e. 200mg three times a day). Amiodarone hydrochloride should then be phased out gradually.

Paediatric population

The safety and efficacy of amiodarone in children and adolescents has not been established. Currently available data are described in sections 5.1 and 5.2. Due to the presence of benzyl alcohol, intravenous Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion is contraindicated in neonates, infants and children up to 3 years old.

Elderly

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

Cardiopulmonary resuscitation

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

See section 6.2 for information on incompatibilities

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 use.

Via infusion: For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance, iodine or to any of the excipients listed in section 6.1. (One ampoule contains approximately 56 mg iodine.)
- Due to the presence of benzyl alcohol, intravenous Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion is contraindicated in neonates.
- Severe respiratory failure, circulatory collapse, or severe arterial hypotension; hypotension, heart failure and cardiomyopathy are also contraindications when using Amiodarone Hydrochloride 50 mg/ml as a bolus injection.
- 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 prolong the QT interval (see section 4.5).
- Pregnancy and lactation. The use is allowed only in special life-threatening circumstances as specified in sections 4.1, 4.4 and 4.6.

The above contraindications do not apply to the use of amiodarone hydrochloride for cardiopulmonary resuscitation of shock-resistant ventricular fibrillation.

4.4 Special warnings and precautions for use

Contains benzyl alcohol (22.2 mg/ml).

Benzyl alcohol may cause toxic and allergic reactions. The minimum amount of benzyl alcohol at which toxicity may occur is not known with an increased risk in young children due to accumulation.

The administration of medications containing benzyl alcohol to newborns or premature neonates has been associated with serious adverse events and a fatal "Gasping Syndrome" (symptoms include a striking onset of gasping syndrome, hypotension, bradycardia and cardio-vascular collapse). This medicinal product is contraindicated in neonates (see section 4.3) and should be used with caution in infants and young children up to 3 years old (see section 4.2).

As benzyl alcohol may cross the placenta, this medicinal product should be used with caution in pregnancy (see section 4.3 and 4.6).

High volumes of medications containing benzyl alcohol should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

Administration:

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

Intravenous infusion is preferred to intravenous bolus due to the haemodynamic effects sometimes associated with rapid injection (see section 4.8). Circulatory collapse may be precipitated by too rapid administration or overdosage (atropine has been used successfully in such patients presenting with bradycardia). Repeated or continuous infusion via peripheral veins may lead to injection site reactions (see section 4.8). When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended.

Amiodarone should not be mixed with other preparations in the same syringe and should not be injected with other preparations in the same line. If treatment with amiodarone should be continued, this should be via intravenous infusion (see section 4.2).

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

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

Reports of crystallisation have been received for hameln Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion:

- Inspect each ampoule and check for crystalline content prior to administration. The solution should only be used if it is clear, free from particles and the container is undamaged and intact.
- Consider the use of in-line filters as an additional precautionary measure.

<u>Cardiac disorders:</u>

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

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

Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during 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.

Severe bradycardia and heart block after sofosbuvir

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.

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.

General anaesthesia:

Caution is advised in patients undergoing general anaesthesia, or receiving high dose oxygen therapy.

Potentially severe complications have been reported in patients taking amiodarone undergoing general anaesthesia: bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output (see section 4.5).

Endocrine disorders (see section 4.8):

Amiodarone may induce hyperthyroidism, particularly in patients with a personal history of thyroid disorders or patients who are taking/have previously taken oral amiodarone. 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.

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):

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

Severe hepatocellular insufficiency may occur within the first 24 hours of IV amiodarone, and may sometimes be fatal. Close monitoring of transaminases is therefore recommended as soon as amiodarone is started.

Severe bullous reactions:

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

Eye disorders (see section 4.8):

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs inducing "Torsade de Pointes" or prolonging the QT interval
Some of the more important drugs that interact with amiodarone include warfarin, digoxin, phenytoin and any drug which prolongs the QT interval.

Combined therapy with the following drugs which prolong the QT interval is contra-indicated (see section 4.3) due to the increased risk of torsade de pointes; 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;
- some anti-psychotics e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpiride and sertindole;
- lithium and tricyclic anti-depressants e.g. doxepin, maprotiline, amitriptyline;
- certain antihistamines e.g. terfenadine, astemizole, mizolastine;
- anti-malarials e.g. quinine, mefloquine, chloroquine, halofantrine;
- moxifloxacin.

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.
- Sofosbuvir: 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).

- 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 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 (e.g. rhabdomyolysis) is increased by concomitant administration of amiodarone with statins metabolised by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolised by CYP 3A4 when given with amiodarone.
- Other drugs metabolised by cytochrome P450 3A4: examples of such drugs are lidocaine, 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.

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.

Lactation

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						- 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.	Angioneurotic oedema (Quincke's

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)
						oedema)
Endocrine disorders					Syndrome of inappropriate antidiuretic hormone secretion (SIADH).	-Hyperthyroidism, sometimes fatal (see section 4.4). -Hypothyroidism.
Psychiatric disorders		Libido decreased				- Delirium (including confusion). - Hallucination
Nervous system disorders		Extrapyramidal tremor.	Peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the drug.		- Benign intracranial hypertension (pseudo-tumour cerebri). - 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 may be associated with colored halos in dazzling light or blurred vision. They usually regress 6-12 months after discontinuation of amiodarone hydrochloride.					Optic neuropathy/ neuritis that may progress to blindness (see section 4.4).
Cardiac disorders		Dose-dependent bradycardia.			- Severe bradycardia (in cases of sinus node dysfunction and in the elderly) or (more rarely) sinus arrest: this may necessitate	Torsades de pointes (see section 4.4)

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)
					discontinuation of the treatment. - Occurrence of new - and exacerbation of existing - arrhythmias, sometimes followed by cardiac arrest (see also section 4.4 and section 4.5). - Conduction disturbances (sinoatrial block, AV block).	
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 too rapid administration (bolus injection).			Hot Flushes.	
Respiratory, thoracic and mediastinal disorders					- Interstitial pneumonitis or fibrosis, sometimes fatal (see section 4.4). - Acute adult respiratory distress syndrome, sometimes with fatal sequelae. - Bronchospasm and/or apnoea	

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)
					in patients with serious respiratory problems, especially patients with asthma.	
Gastrointestinal disorders					Nausea.	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).	
Skin and subcutaneous tissue disorders		Eczema.			Sweating.	- Urticaria. - Severe skin reaction as toxic epidermal necrolysis (TEN)/Stevens-Johnson syndrome (SJS), bullous dermatitis and Drug reaction with eosinophilia and systematic symptoms (DRESS).
Musculoskel						Back pain.

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)
etal and Connective Tissue Disorders						
Reproductive system and breast disorders						Libido decreased
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.		The excipient benzyl alcohol may cause hypersensitivity reactions.		
Injury, poisoning and procedural complications						Primary graft dysfunction post cardiac transplant (see section 4.4).

A few rare cases with various clinical symptoms, indicative of hypersensitivity reactions, have been reported: vasculitis, reduced renal function with a rise in creatinine levels, thrombocytopenia, anaphylaxis.

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

4.9 Overdose

There is no information regarding overdosage with intravenous amiodarone.

In cases of acute overdose or too rapid intravenous administration, the following can be observed: nausea, vomiting, constipation, sweating, bradycardia 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.

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

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.

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.

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 glucose 5% 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 refractory to 3 or more defibrillator shocks, epinephrine and another defibrillator shock, or with recurrent ventricular fibrillation after initial successful defibrillation – were given either amiodarone (5 mg/kg) or lidocaine (1.5 mg/kg). Amiodarone significantly increased the chances of resuscitation and hospital admission: 22.8% in the group receiving amiodarone (41 out of 180 patients) versus 12% in the group receiving lidocaine (20 out of 167 patients), $p = 0.009$. After adjustment for other factors affecting survival, the adjusted ratio for survival to hospital admission was 2.49 (95% confidence interval, 1.28 to 4.85; $p = 0.007$) in the group receiving amiodarone, compared with the group receiving lidocaine. The percentage of patients sustaining cardiac arrest after administration of the initial study medication, after defibrillation, was significantly higher in the group receiving lidocaine (28.9%) than in the group receiving amiodarone (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

Amiodarone has a slow elimination rate and a marked affinity for tissue. Absorption of amiodarone hydrochloride from the gastrointestinal tract following oral administration is 50 %. After a single dose plasma levels will be reached in 3-7 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.

Intravenous administration

After injection the maximal effect is reached after 15 minutes. 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 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 renaly.

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 led to pulmonary damage (fibrosis, phospholipidosis; in hamsters, rats and dogs). Pulmonary toxicity appears to result from radical formation and perturbation of cellular energy production. In addition, amiodarone caused liver damage in rats. Regarding the genotoxicity aspects the in vitro Ames test and in vivo mouse bone marrow micronucleus test have been conducted. Both studies yielded negative results.

In a 2-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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80 (E433)

Benzyl alcohol

Water for injections

6.2 Incompatibilities

Amiodarone hydrochloride is incompatible with saline solution and may only be administered in a glucose 5% solution.

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, diluted 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.

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

6.3 Shelf life

Unopened ampoules: 2 years

Prepared solutions:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.

Keep the ampoules 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

Each folding box contains 5 ml clear glass ampoules, type I, with 3 ml sterile concentrate.

Pack sizes:

5, 10 x 5 ml ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reports of crystallisation have been received for hameln Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion. Before use, the sterile concentrate should be visually inspected for clarity, particulate matter, discolouration and the integrity of the container. The solution should only be used if it is clear, free from particles and the container is undamaged and intact. Consider the use of in-line filters as an additional precautionary measure.

Prior to administration by intravenous infusion, Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion should be diluted according to directions with glucose 5%. One ampoule of Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion diluted as recommended in 250 ml of glucose 5% results in a concentration of 0.6 mg/ml of amiodarone hydrochloride.

Administer 5 mg per kg body weight in 250 ml of glucose 5% solution over 20 minutes to 2 hours.

On account of the stability of the solution, do not use concentrations below 300 mg per 500 ml and do not add other medicinal products to the infusion fluid (see section 4.2).

For single use only.

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

7 MARKETING AUTHORISATION HOLDER

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