# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Amiodarone 30 mg/ml solution for injection/infusion in pre-filled syringe

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 30 mg amiodarone hydrochloride.

Each 10 ml pre-filled syringe contains 300 mg amiodarone hydrochloride.

Excipient(s) with known effect:
Each pre-filled syringe contains
-20 mg/ml of benzyl alcohol.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection/infusion in pre-filled syringe

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

– Tachyarrhythmias associated with Wolff-Parkinson-White syndrome.

– All types of tachyarrhythmias including supraventricular, nodal and ventricular tachycardias; atrial flutter and fibrillation; ventricular fibrillation; when other drugs cannot be used.

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

## 4.2 Posology and method of administration

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

Amiodarone may be used prior to DC cardioversion.

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% w/v dextrose. This may be followed by repeat infusion up to 1200mg (approximately 15mg/kg bodyweight) in up to 500ml 5% w/v dextrose 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 injection of 150-300mg in 10-20ml 5%w/v dextrose over a minimum of 3 minutes. This should not be repeated for at least 15 minutes. Patients treated in this way with amiodarone must be closely monitored, e.g. in an intensive care unit (see section 4.4).

*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 injection should then be phased out gradually.

*Paediatric population:*
The safety and efficacy of amiodarone in children has not been established.

Currently available data are described in sections 5.1 and 5.2.

Because of the content of benzyl alcohol, intravenous administration of amiodarone should be used with caution in neonates and children < 3 years (see section 4.4).

*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 20ml 5% w/v dextrose 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.

## 4.3 Contraindications

- Known hypersensitivity to the active substance, iodine or to any of the excipients listed in section 6.1 (one pre-filled syringe contains approximately 112mg 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 conjunction with a pacemaker.
- 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 induce torsades de pointes is contra-indicated (see section 4.5).
- Pregnancy - except in exceptional circumstances (see section 4.6).
- Lactation (see section 4.6).

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

## 4.4 Special warnings and precautions for use

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

IV infusion is preferred to bolus due to the haemodynamic effects sometimes associated with rapid injection (see section 4.8). Circulatory collapse may be precipitated by too rapid administration or overdosage (atropine has been used successfully in such patients presenting with bradycardia).

Do not mix other preparations in the same syringe. Do not inject other preparations in the same line. If amiodarone should be continued, this should be via intravenous infusion (see section 4.2).

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

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

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

<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 digitalis therapy. In these circumstances, amiodarone treatment should be withdrawn. If necessary beta-adreno-stimulants 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 (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.

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

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

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

Endocrine disorders (see section 4.8):

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

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

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 treatment. 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).

Hepatobiliary 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.

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.

Benzyl alcohol
This medicine contains 200mg benzyl alcohol in each 10ml pre-filled syringe, which is equivalent to 20mg/ml. Benzyl alcohol may cause allergic reactions.

Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("Gasping Syndrome"). The minimum amount of benzyl alcohol at which toxicity may occur is not known. Increased risk due to accumulation in young children.

High volumes 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).

High volumes of benzyl alcohol should be used with caution and only if necessary during pregnancy or breast□feeding. This is because large amounts of benzyl alcohol can accumulate and may cause side effects (called 'metabolic acidosis').

## 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 torsades 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, amisulpride and sertindole
- lithium and tricyclic anti-depressants e.g. doxepin, maprotiline, amitriptyline
- certain antihistamines e.g. terfenadine, astemizole, mizolastine
- anti-malarials e.g. quinine, mefloquine, chloroquine, halofantrine
- 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.
- Stimulant laxatives, which 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: e.g. diuretics, systemic corticosteroids, 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
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.

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.

Effect of amiodarone on other medicinal products

Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP1A1, CYP1A2, CYP3A4, CYP2C9, CYP2D6 and P-glycoprotein and may increase exposure of their substrates.

Due to the long half-life of amiodarone, interactions may be observed for several months after discontinuation of amiodarone.

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

Digoxin
Administration of amiodarone to a patient already receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels; disturbances in automaticity (excessive bradycardia), a synergistic effect on heart rate and atrioventricular conduction may occur. Clinical, ECG and biological monitoring is recommended to observe for signs of digitalis toxicity and digoxin dosage should be halved.

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 and ergotamine and colchicine.

Interaction with substrates of other CYP 450 isoenzymes
In vitro studies show that amiodarone also has the potential to inhibit CYP1A2, CYP2C19 and CYP2D6 through its main metabolite. When co-administered, amiodarone would be expected to increase the plasma concentration of drugs whose metabolism is dependent upon CYP1A2, CYP2C19 and CYP2D6.

Effect of other products on amiodarone
CYP3A4 inhibitors and CYP2C8 inhibitors may have a potential to inhibit amiodarone metabolism and to increase its exposure.

It is recommended to avoid CYP 3A4 inhibitors (e.g. grapefruit juice and certain medicinal products) during treatment with amiodarone.

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

Other drug interactions with amiodarone (see section 4.4)
Coadministration of amiodarone with sofosbuvir-containing regimens may lead to serious symptomatic bradycardia. The mechanism for this bradycardia effect is unknown.

If coadministration cannot be avoided, cardiac monitoring is recommended (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There is insufficient data on the use of amiodarone during pregnancy in humans to judge any possible toxicity. However, in view of its effect on the fetal thyroid gland, amiodarone is contraindicated during pregnancy, except in exceptional circumstances.

Breast-feeding

Amiodarone is excreted into the breast milk in significant quantities and breast-feeding is contraindicated.

Fertility

Treatment with amiodarone has been associated with epididymitis in men. In animal fertility studies reduction in male and female fertility was observed.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

## 4.8 Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention: very common (> = 10%), common (≥ 1% and < 10%); uncommon (≥ 0.1% and < 1%); rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), 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
- Frequency not known: Neutropenia, agranulocytosis

Cardiac disorders:

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

- Frequency not known Torsade de pointes (see 4.4 and 5.1).

Eye disorders:
- Frequency not known: Optic neuropathy/neuritis that may progress to blindness (see section 4.4).

Endocrine disorders:
- Frequency not known: Hyperthyroidism (see section 4.4).
- Very rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Gastrointestinal disorders:
- Very rare: nausea.
- Pancreatitis /acute pancreatitis

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.

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

Immune system disorders:
- Very rare: anaphylactic shock.
- Frequency not known: Angioneurotic oedema (Quincke's Oedema)

Musculoskeletal and Connective Tissue Disorders
- Frequency not known: Back pain

Nervous system disorders:
- Very rare: benign intra-cranial hypertension (pseudo tumor cerebri), headache.

Respiratory, thoracic and mediastinal disorders:
- Very rare:
  - interstitial pneumonitis or fibrosis, sometimes fatal (see section 4.4)
  - severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal (see sections 4.4 and 4.5)
  - bronchospasm and/or apnoea in case of severe respiratory failure, and especially in asthmatic patients.

Psychiatric disorders:
- Frequency not known: Delirium /Confusional state, hallucination, libido decreased.

Skin and subcutaneous tissue disorders:
- Common: eczema
- Very rare: sweating.
- Frequency not known: Urticaria, severe skin reactions sometimes fatal including toxic epidermal necrolysis (TEN)/Stevens- Johnson syndrome (SJS), bullous dermatitis and Drug reaction with eosinophilia and systematic symptoms (DRESS).

Vascular disorders:

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

Injury, poisoning and procedural complaints:

- *Not known:* primary graft dysfunction post cardiac transplant (see section 4.4).

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 Google Play or Apple App Store.

### 4.9 Overdose

There is no information regarding overdosage with intravenous amiodarone.

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

In the event of overdose, treatment should be symptomatic, in addition to general supportive measures. The patient should be monitored and if bradycardia occurs beta-adrenostimulants or glucagon may be given.

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

Neither amiodarone nor its metabolites are dialysable.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: - Antiarrhythmic

ATC code: - C01B D01

Amiodarone injection is a product for the treatment of tachyarrhythmias and has complex pharmacological actions. Its effects are anti-adrenergic (partial α- and β-blockers). It has haemodynamic effects (increased blood flow and systemic/coronary vasodilation). The drug reduces myocardial oxygen consumption and has been shown to have a sparing effect of rat myocardial ATP utilisation, with decreased oxidative processes. Amiodarone inhibits the metabolic and biochemical effects of catecholamines on the heart and inhibits $Na^+$ and $K^+$ activated ATP-ase.

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 is metabolised mainly by CYP3A4, and also by CYP2C8, however the pharmacokinetics of amiodarone are unusual and complex, and have not been completely elucidated.

Absorption following oral administration is variable and may be prolonged, with enterohepatic cycling. The major metabolite is desethylamiodarone. Amiodarone is highly protein bound (> 95%). Renal excretion is minimal and faecal excretion is the major route. A study in both healthy volunteers and patients after intravenous administration of amiodarone reported that the calculated volumes of distribution and total blood clearance using a two-compartment open model were similar for both groups. 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. A bolus IV injection of 400mg gave a terminal $T^{½}$ of approximately 11 hours.

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

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 a 2-years carcinogenicity study in rats, amiodarone caused an increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinically 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

Benzyl alcohol

Polysorbate 80

Water for Injections

### 6.2 Incompatibilities

Amiodarone is incompatible with saline and should be administered solely in a 5% w/v dextrose solution. Amiodarone injection, diluted with 5% dextrose solution to a concentration of less than 0.6mg/ml, is unstable. Solutions containing less than 1 pre-

filled syringe of amiodarone in 500ml dextrose 5% are unstable and should not be used.

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.

## 6.3 Shelf life

2 years

From a microbiological point of view, unless the method of opening and dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

## 6.4 Special precautions for storage

Do not store above 25°C. Store the syringe in the outer carton until needed.

## 6.5 Nature and contents of container

10 ml clear glass pre-filled syringe with plunger stopper and plunger rod.

Pack size: 1 pre-filled syringe

## 6.6 Special precautions for disposal

Refer section 4.2.

For single use only. Discard any unused medicinal product after opening.

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

## 7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
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Whiddon Valley
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EX32 8NS

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/1267

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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## 10 DATE OF REVISION OF THE TEXT

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