Initial submission: 19/10/2020
Response to Clinical Recommendations as per email received 13/07/2021: submitted 30/07/2021
Response to P&A Recommendations as per email received 03/02/2023: submitted 15/03/2023

CLEAN AMENDED PROPOSED PROFESSSIONAL INFORMATION

1.	**SCHEDULING STATUS**
2.	S4
3.	
4.	**1. NAME OF THE MEDICINE**
5.	**ACCORD AMIODARONE 30 mg/ml Pre-filled syringe**
6.	Solution for injection or infusion
7.	
8.	**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
9.	Each ml of solution contains 30 mg Amiodarone
10.	Excipients: benzyl alcohol, polysorbate 80, water for injection
11.	For the full list of excipients, see section 6.1.
12.	
13.	**3. PHARMACEUTICAL FORM**
14.	A clear, colourless to pale yellow solution
15.	
16.	**4. CLINICAL PARTICULARS**
17.	**4.1 Therapeutic indications**
18.	• Tachydysrhythmias associated with Wolff-Parkinson-White syndrome and other types
19.	of tachydysrhythmias of paroxysmal nature including supraventricular, nodal and
20.	ventricular tachycardias
21.	• Atrial flutter and atrial fibrillation
22.	• Ventricular fibrillation which has not responded to other antidysrhythmic therapy
23.	

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4.2 Posology and method of administration

Posology

ACCORD AMIODARONE 30 mg/ml is incompatible with saline and should be administered only in 5 % dextrose.

The use of medical equipment or devices containing plasticiser such as DEHP (di-2-ethylhexyl phthalate) in the presence of **ACCORD AMIODARONE 30 mg/ml** results in leaching out of DEHP. In order to minimise patient exposure to DEHP, the final dilution for infusion may preferably be administered through non DEHP-containing sets.

ACCORD AMIODARONE 30 mg/ml should only be used when facilities exist for cardiac monitoring or defibrillation, should the need arise.

The recommended dose is 5 mg/kg body mass given by intravenous infusion over a period of 20 minutes to 2 hours, administered as a dilute solution in 250 ml 5 % dextrose. This may be followed by repeat infusions up to 1 200 mg (approximately 15 mg/kg body mass) in up to 500 ml 5 % dextrose per 24 hours, the rate of infusion being adjusted on the basis of clinical response. **ACCORD AMIODARONE 30 mg/ml** may, at the discretion of the healthcare professional, be given as a bolus injection of 150 mg - 300 mg in 10 - 20 ml over a minimum of 3 minutes. This should not be repeated for at least 15 minutes. Patients treated in this way must be closely monitored e.g. in an intensive care unit.

When given by infusion, **ACCORD AMIODARONE 30 mg/ml** may reduce drop size and, if appropriate, adjustments should be made to the rate of infusion.

Maintenance therapy

Oral therapy should be initiated concomitantly at the usual loading dose as soon as possible after an adequate response is obtained and the intravenous therapy gradually phased out.

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Repeated or continuous infusion via peripheral veins may lead to local discomfort and inflammation. When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended.

Special populations

Use in the elderly

It is important that the minimum effective dose is used. There is no evidence that dosage requirements are different for elderly patients, and they may be more susceptible to bradycardia and conduction defects if too high a dose is employed.

Method of administration

For intravenous injection or infusion

4.3 Contraindications

- Hypersensitivity to amiodarone, iodine or to any of the other ingredients of **ACCORD AMIODARONE 30 mg/ml** listed in section 6.1.
- **ACCORD AMIODARONE 30 mg/ml** should not be used prophylactically in the preoperative period of cardio-pulmonary surgery.
- 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, **ACCORD AMIODARONE 30 mg/ml** should be used in conjunction with a pacemaker.
- Severe respiratory failure, circulatory collapse and severe arterial hypotension.
- Congestive heart failure is also a contra-indication when using as a bolus injection.
- Concomitant administration of amiodarone with medicines which may prolong the QT interval.

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72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83.	• Latent or manifest heart failure may be worsened and, in this case **ACCORD AMIODARONE 30 mg/ml** should be associated with the usual cardiotonic and diuretic treatments. • Thyroid dysfunction • 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 digoxin therapy. In these circumstances, **ACCORD AMIODARONE 30 mg/ml** treatment should be withdrawn. If necessary, beta-adrenostimulants or glucagon may be given. • Pregnancy and lactation • Paediatric patients
84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95.	**4.4 Special warnings and precautions for use** **Administration** **ACCORD AMIODARONE 30 mg/ml** should only be used in a special care unit under continuous monitoring (ECG and blood pressure). IV infusion is preferred to an 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. When given by infusion amiodarone hydrochloride may reduce drop size and, if appropriate, adjustments should be made to the rate of infusion.

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Anaesthesia

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

Cardiac disorders

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

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 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.

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

The pharmacological action of amiodarone induces ECG changes

QT prolongation (related to prolonged repolarisation) with the possible development of U-waves and deformed Twaves; these changes do not reflect toxicity.

General anaesthesia

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

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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

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-T3, free-T4, usTSH) remain interpretable.

Amiodarone inhibits peripheral conversion of thyroxine (T4) to triiodothyronine (T3) 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.

Both hyper- and hypothyroidism have occurred during, or soon after, treatment with **ACCORD AMIODARONE 30 mg/ml**. Simple monitoring of the usual biochemical tests is confusing because some (PBI and ^{131}I uptake) are invalidated and others (T_4, T_3 and FTI) may be altered where the patient is clearly euthyroid.

Clinical monitoring is therefore recommended and should be continued for some months after discontinuation of amiodarone treatment. This is particularly important in the elderly. In patients whose history indicates an increased risk of thyroid dysfunction, regular testing is

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recommended.

Clinical features of hyperthyroidism such as mass loss, asthenia, restlessness, increase in heart rate or a recurrence of the cardiac dysrhythmia, angina or congestive heart failure, should alert the clinician.

The diagnosis may be supported by the finding of an elevated serum tri-iodothyronine (T_3), a low level of thyroid stimulating hormone (TSH as measured by high sensitivity methods) and a reduced TSH response to thyrotrophin releasing hormone (TRH). Elevation of reverse T_3(rT_3) may also be found.

The clinical features of hypothyroidism such as mass gain and reduced activity or excessive bradycardia should alert the clinician. The onset may be abrupt. The diagnosis may be supported by the presence of an elevated serum TSH level and an exaggerated TSH response to TRH. The thyroxine (T_4), T_3 and free thyroxine index (FTI) may be low.

In the case of hyperthyroidism, **ACCORD AMIODARONE 30 mg/ml** should be withdrawn.

Courses of anti-thyroid medication have been used for the treatment of severe thyroid hyperactivity, large doses may be required initially. These may not always be effective and concomitant high dose corticosteroid therapy may be required for several weeks.

Thyroid hypofunction usually resolves within 3 months of cessation of **ACCORD AMIODARONE 30 mg/ml**; it may be treated cautiously with L-thyroxine.

Concomitant use of **ACCORD AMIODARONE 30 mg/ml** should only be used in life threatening situations, when TSH levels may provide a guide to L-thyroxine dosage.

Respiratory, thoracic and mediastinal disorders

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

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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.

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

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 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 sofosbuvir-containing regimens when other alternative anti-dysrhythmic 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

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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 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.

Porphyria

ACCORD AMIODARONE 30 mg/ml should be avoided in porphyria as it may precipitate an attack.

Medicine interactions

Concomitant use of amiodarone with the following medicines is not recommended:

beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem), stimulant laxative medicines which may cause hypokalaemia.

In cases of hypokalaemia, corrective action should be taken and QT interval monitored. In case of torsade de pointes antidysrhythmic medicines 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.

Benzyl alcohol

ACCORD AMIODARONE 30 mg/ml contains benzyl alcohol in each 10 ml syringe and may cause 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 medicines containing benzyl alcohol to newborns or premature

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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).

As benzyl alcohol may cross the placenta, this medicine should be used with caution in pregnancy.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment or those who are pregnant or breast-feeding because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction with other medicinal products and other forms of interaction

Medicines inducing "Torsade de Pointes" or prolonging the QT interval

Some of the more important medicines that interact with amiodarone include warfarin, digoxin, phenytoin and any medicines which prolongs the QT interval.

Combined therapy with the following medicines 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-dysrhythmic medicines e.g. quinidine, procainamide, disopyramide
- Class III anti-dysrhythmic medicines 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

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Fluoroquinolones

There have been 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).

Medicines lowering heart rate, causing automaticity or conduction disorders

Combined therapy with the following medicines is not recommended;

- Beta blockers and certain calcium channel blockers (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 medicines which may also cause hypokalaemia and/or hypomagnesaemia should be considered with caution:

i. diuretics,
ii. systemic corticosteroids,
iii. tetracosactide,
iv. 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 anaesthesia. (see section 4.4)

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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.

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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 medicines 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.

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Other medicines metabolised by cytochrome P450 3A4: examples of such medicines are lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine, ergotamine and colchine.

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 medicines 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 medicine 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

Women of childbearing potential

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.

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336.	**Pregnancy**
337.	Amiodarone and N-desmethylamiodarone cross the placental barrier and achieve 10-25 % of
338.	the maternal plasma concentrations in the infant. Most frequent complications include
339.	impaired growth, preterm birth and impaired function of the thyroid gland in newborn babies.
340.	Hypothyroidism, bradycardia and prolonged QT intervals were observed in approximately 10
341.	% of the newborn babies. In isolated cases an increased thyroid gland or cardiac murmurs
342.	were found. The malformation rate does not appear to be increased. However, the possibility
343.	of cardiac defects should be kept in mind. Therefore, amiodarone is contra-indicated during
344.	pregnancy (see section 4.3).
345.	**Breast-feeding**
346.	Amiodarone and its active metabolite are excreted into the breast milk in significant quantities.
347.	**ACCORD AMIODARONE 30 mg/ml** is contraindicated during lactation (see section 4.3).
348.	If therapy is required during the lactation period, or if amiodarone was taken during
349.	pregnancy, breast-feeding should be stopped. The use is allowed only in special life-
350.	threatening circumstances as specified in sections 4.1, 4.3 and 4.4.
351.	**Fertility**
352.	Elevated serum levels of Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH)
353.	were found in male patients after long-term treatment indicating testicular dysfunctions
354.	
355.	**4.7 Effects on ability to drive and use machines**
356.	**ACCORD AMIODARONE 30 mg/ml** may affect the ability to drive or use machinery.
357.	
358.	**4.8 Undesirable effects**
359.	**Summary of safety profile**

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

Tabulated list of undesirable effects

Table 1: Undesirable effects as per System Organ Class

SYSTEM ORGAN CLASS	INCIDENCE	ADVERSE REACTION
Blood and lymphatic system disorders	Less frequent	Haemolytic anaemia, thrombocytopenia
	Frequency unknown	Bone marrow granulomas
Immune system disorders	Less frequent	Anaphylactic shock, angiooedema
Endocrine disorders	Less frequent	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
	Frequency unknown	Hyperthyroidism, sometimes fatal (see section 4.4), hypothyroidism
Psychiatric disorders	Frequency unknown	Delirium (including confusion)
	Frequent	Extrapyramidal tremor

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Nervous system disorders	Less frequent	Peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the medicine, benign intracranial hypertension (pseudotumour cerebri), headache, nightmares, vertigo and sleeplessness
Eye disorders	Frequent	Microdeposits[1]
	Less frequent	Optic neuropathy / neuritis that may progress to blindness.
Cardiac disorders	Frequent	Dose-dependent bradycardia
	Less frequent	Severe bradycardia (in cases of sinus node dysfunction and in the elderly) or (more rarely) sinus arrest: this may necessitate discontinuation of the treatment, occurrence of new - and exacerbation of existing -arrhythmias, including atypical ventricular tachycardias (Torsades de Pointes) sometimes followed by cardiac arrest (see also section 4.4 and section 4.5), conduction disturbances (sinoatrial block, AV block).
Vascular disorders	Frequent	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).

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	Less frequent	Hot flushes
Respiratory, thoracic and mediastinal disorders	Less frequent	Interstitial pneumonitis (see section 4.4), acute adult respiratory distress syndrome, sometimes with fatal sequelae, bronchospasm and/or apnoea in patients with serious respiratory problems, especially patients with asthma.
Gastro-intestinal disorders	Less frequent	Nausea
	Frequency unknown	Pancreatitis (acute)
Hepato-biliary disorders	Less frequent	A mild to moderate increase in transaminase levels[2], 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	Frequent	Eczema
	Less frequent	Sweating
	Frequency unknown	Urticaria, severe skin reaction as toxic Epidermal necrolysis (TEN)/Stevens-Johnson syndrome (SJS), bullous dermatitis and drug reaction with eosinophilia and systematic symptoms (DRESS)

Musculo-skeletal and connective tissue disorders	Frequency unknown	Back pain
General disorders and administration site conditions	Frequent	At the site of injection or infusion: pain, erythema, oedema, necrosis, extravasation, infiltration, inflammation, induration, thrombophlebitis, phlebitis, cellulitis, infection, pigmentation changes
	Less frequent	The excipient benzyl alcohol may cause hypersensitivity reactions.

Description of selected adverse reactions

1. 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.

2. 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.

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.

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456.	Reporting of suspected adverse reactions
457.	Reporting suspected adverse reactions after authorisation of the medicine is important. It
458.	allows continued monitoring of the benefit/risk balance of the medicine. Healthcare
459.	professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04
460.	Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:
461.	https://www.sahpra.org.za/Publications/Index/8
462.	
463.	**4.9 Overdose**
464.	In cases of acute overdose or too rapid intravenous administration, the following can be
465.	observed: nausea, vomiting, constipation, sweating, bradycardia and prolonged QT interval.
466.	Atropine has been used successfully in patients presenting with bradycardia. Following
467.	substantial overdose, onset of hypotension, heart block and Torsades de Pointes should also
468.	be expected. In exceptional cases, hyperthyroidism may occur.
469.	Few cases of sinus bradycardia, heart block, attacks of ventricular tachycardia, torsades de
470.	pointes, circulatory failure and hepatic injury have been reported.
471.	Following substantial overdose, prolonged ECG monitoring must be performed. Intensive care
472.	unit admission should be considered. Hypotension can be treated with infusion fluids or
473.	vasopressors. The use of alpha- or beta-adrenergic medicines or temporary pacing may be
474.	indicated. Class Ia and III antiarrhythmic medicines should be avoided, as they are associated
475.	with QT interval prolongation and induction of Torsades de Pointes. Further treatment should
476.	be supportive and symptomatic.
477.	The patient should be monitored and if bradycardia occurs beta - adrenostimulants or
478.	glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also
479.	occur.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, antidysrhythmics, class III

ATC Code: CO1BDO1

Amiodarone is a di-iodinated benzofuran derivative and is classified as a class III antidysrhythmic medicine 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-dysrhythmias 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

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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 (rT_3) and decreases in serum triiodothyronine (T_3) as a result of inhibition of deiodination of T_4 to T_3 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.

5.2 Pharmacokinetic properties

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

Intravenous administration

After injection the maximal effect is reached after 15 minutes.

Distribution

After this time there is distribution into the tissue and a fast decrease of the plasma level within 4 hours. To achieve saturation of the tissue treatment needs to be continued intravenously or orally.

During saturation amiodarone is accumulated particularly in the fat tissue and steady state is reached within a period of one to several months.

Because of these characteristics the recommended saturating dosage should be given in order to reach fast saturation of the tissue which is the prerequisite for therapeutic efficacy.

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Biotransformation

Amiodarone is highly protein bound (> 95%). Amiodarone hydrochloride has a long half-life which varies interindividually between 20 and 100 days.

Elimination

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. 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.

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 clinically relevant exposures. Since mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is

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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 injection

6.2 Incompatibilities

Amiodarone is incompatible with saline and should be administered solely in a 5 % w/v dextrose solution.

Amiodarone, diluted with 5 % dextrose solution to a concentration of less than 0.6 mg/ml, is unstable. Solutions containing less than 1 pre-filled syringe of amiodarone in 500 ml 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 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.

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576.	**6.3 Shelf life**
577.	2 years
578.	From a microbiological point of view, the product should be used immediately.
579.	For single use only.
580.	Any unused solution from the opened syringes should be discarded.
581.	Keep out of reach of children.
582.	
583.	**6.4 Special precautions for storage**
584.	Store at or below 25 °C.
585.	Store the syringe in the outer carton until needed for use.
586.	
587.	**6.5 Nature and contents of container**
588.	10 ml glass pre-filled syringe with plunger stopper and plunger rod.
589.	Pack size: 1, 5 or 10 syringes per carton
590.	Not all pack sizes may be marketed
591.	
592.	**6.6 Special precautions for disposal and other handling**
593.	**ACCORD AMIODARONE 30 mg/ml** is intended for single dose use only.
594.	Any unused solution should be discarded immediately after initial use.
595.	Before use, the sterile concentrate should be visually inspected for clarity, particulate matter,
596.	discolouration and the integrity of the container. The solution should only be used if it is clear
597.	or slightly yellow and the container is undamaged and intact.
598.	Prior to administration by intravenous infusion this product should be diluted according to
599.	directions with the recommended infusion fluid (see section 6.2).

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600. 601. 602.	Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
603. 604. 605. 606. 607. 608. 609. 610.	**7. HOLDER OF CERTIFICATE OF REGISTRATION** Accord Healthcare (Pty) Limited Building 2, Tuscany Office Park 6 Coombe Place Rivonia Johannesburg South Africa
611. 612. 613.	**8. REGISTRATION NUMBER(S)** **55/6.2/0465**
614. 615. 616.	**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** 06 June 2023
617. 618. 619.	**10. DATE OF REVISION OF THE TEXT** **06 June 2023**