Prescribing Information for Amiodarone 30mg/ml Injection

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.
Presentation: Clear, slightly yellow solution in a glass prefilled syringe containing 30mg of amiodarone hydrochloride per ml of solution. **Indications:** Treatment should be initiated and normally monitored only under hospital or specialist supervision. Amiodarone is indicated only for the treatment of severe cardiac rhythm disorders not responding to other therapies or when other treatments cannot be used: AV nodal arrhythmias and AV re-entrant tachycardia, e.g. as a manifestation of Wolff-Parkinson-White syndrome, and all types of tachyarrhythmias including supraventricular, nodal and ventricular tachycardias; atrial flutter and fibrillation; life-threatening ventricular arrythmias (including persistent or non-persistent ventricular tachycardia or episodes of ventricular fibrillation). Amiodarone hydrochloride 30mg/ml injection can be used where a rapid response is required or where oral administration is not possible. Amiodarone may be used prior to DC cardioversion. **Dosage and administration:** For intravenous injection or infusion. Infusion: For instructions on dilution of the medicinal product before administration, consult section 6.6 of the SmPC. Amiodarone should only be used when facilities exist for cardiac monitoring, defibrillation, and cardiac pacing. 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. 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 Warnings and Precautions). *Cardiopulmonary resuscitation:* The recommended dose for ventricular fibrillations/ pulseless ventricular tachycardia resistant to defibrillation is 300 mg (or 5 mg/kg bodyweight) as a rapid injection. An additional 150 mg (or 2.5 mg/kg bodyweight) IV dose may be considered if ventricular fibrillation persists (see Incompatibilities on the SmPC). *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 and adolescents has not been established. Due to the presence of benzyl alcohol, intravenous amiodarone is usually contraindicated in neonates and should be used with caution in infants and children up to 3 years old (see Contra-Indications below). No controlled paediatric studies have been undertaken. In published uncontrolled studies, effective doses for children were: Loading dose: 5mg/kg bodyweight over 20 minutes to 2 hours; Maintenance dose: 10 to 15mg/kg/day from a few hours to several days. If needed, oral therapy may be initiated concomitantly. *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. *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. **Consult SmPC for additional information. Contra-Indications:** Hypersensitivity to the active substance, iodine (one pre-filled syringe contains approximately 112mg iodine) or to any of the excipients; 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; evidence or history of thyroid dysfunction; 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 concomitant administration of amiodarone with drugs which may prolong the QT interval (see Interactions); due to the presence of benzyl alcohol, intravenous amiodarone is contraindicated in neonates and should be used with caution in infants and children up to 3 years old (see Warnings and Precautions); pregnancy and lactation – the use is allowed only in special life-threatening circumstances as specified in sections 4.1, 4.4, 4.6 of the SmPC. All these above contra-indications do not apply to the use of amiodarone for cardiopulmonary resuscitation of shock resistant ventricular fibrillation. **Warnings and precautions:** *Administration:* Amiodarone injection should only be used in a special care unit under continuous monitoring (ECG and blood pressure). IV infusion is preferred

to intravenous bolus due to the haemodynamic effects sometimes associated with rapid injection. Circulatory collapse may be precipitated by too rapid administration or overdosage. Repeated or continuous infusion via peripheral veins may lead to injection site reactions (see Undesirable Effects on the SmPC). 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. *Anaesthesia*: Before surgery, the anaesthetist should be informed that the patient is being treated with amiodarone (see Interactions). *Cardiac disorders*: Caution should be exercised in patients with hypotension and decompensated cardiomyopathy and severe heart failure (see Contra-Indications). 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. 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-arrhythmic effect. Onsets of new arrhythmias or worsening of treated arrhythmias, sometimes fatal, have been reported. 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 T-waves; these changes do not reflect toxicity. *General anaesthesia*: Caution is advised in patients undergoing general anaesthesia or receiving high dose oxygen therapy. Potentially severe complications have been reported: see Interactions. *Endocrine disorders:* Amiodarone may induce hyperthyroidism. 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 remain interpretable. Amiodarone inhibits peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause isolated biochemical changes 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 Undesirable Effects on SmPC)*: 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, and corticosteroid therapy should be considered. Clinical symptoms often resolve within a few weeks, although 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. *Hepato-biliary disorders (see Undesirable Effects on SmPC)*: 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. 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, recommend 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. *Drug interactions*: see under Interactions below. *Contains benzyl alcohol (20 mg/ml):* Contains 200mg of benzyl alcohol in each 10ml syringe. Benzyl alcohol 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 medications containing benzyl alcohol to newborns or premature neonates has been associated with serious adverse events and a fatal "Gasping Syndrome". As benzyl alcohol may cross the placenta, this medicinal product 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). **Consult SmPC for additional information.**

Interactions: *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 due to the increased risk of torsade de pointes; for example: Class Ia and Class III anti-arrhythmic drugs; intravenous erythromycin, co-trimoxazole or pentamidine injection; some anti-psychotics such as chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpride and sertindole; lithium and tricyclic anti-depressants; certain antihistamines like for example terfenadine, astemizole, mizolastine; anti-malarials; 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 should be avoided (concomitant use with moxifloxacin is contra-indicated, see above). *Drugs lowering heart rate, causing automaticity or conduction disorders*: Combined therapy with the following drugs is not recommended: beta blockers and certain calcium channel blockers (diltiazem, verapamil); stimulant laxatives. 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 anaesthesia. 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 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: 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*: 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 – a reduction in the dose of ciclosporin may be necessary; *Statins*: the risk of muscular toxicity is increased by concomitant administration of amiodarone with statins metabolised by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolised by CYP 3A4 when given with amiodarone. Other drugs metabolised by cytochrome P450 3A4: examples of such drugs are lidocaine, 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 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. *Other drug interactions with amiodarone (see Warnings and Precautions)*: Coadministration of amiodarone with sofosbuvir-containing regimens may lead to serious symptomatic bradycardia. If coadministration cannot be avoided, cardiac monitoring is recommended. **Consult SmPC for further information. 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, resulting in complication in newborn babies. Therefore, amiodarone must not be used during pregnancy unless clearly necessary and the real risk of reoccurrence of life-threatening arrhythmias should be weighed against the possible hazard for the foetus. Given the long half-life of amiodarone, women of child-bearing age would need to plan for a pregnancy starting at least half a year after finishing therapy, in order to avoid exposure of the embryo/foetus during early pregnancy. *Breast-feeding*: Amiodarone and its active metabolite are excreted into the breast milk in significant quantities. If therapy is required, 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 of the SmPC. *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. **Consult SmPC for further information. Effects on ability to drive and use machines:** Amiodarone hydrochloride may affect the ability to drive or use machines. **Undesirable effects:** The most common adverse drug effects reported with intravenous amiodarone hydrochloride are infusion phlebitis, bradycardia, and hypotension. *Very common (≥1/10)*: 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. *Common (≥1/100 to <1/10)*: extrapyramidal tremor; dose-dependent bradycardia; 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); eczema; at the site of injection or infusion: pain, erythema, oedema, necrosis, extravasation, infiltration, inflammation, induration, thrombophlebitis, phlebitis, cellulitis, infection, pigmentation changes. *Some serious AE with frequency Not known (cannot be estimated from the available data)*: Severe skin reaction as toxic epidermal necrolysis (TEN)/Stevens-Johnson syndrome (SJS), bullous dermatitis and Drug reaction with eosinophilia and systematic symptoms (DRESS). 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. **Consult SmPC for the full list of undesirable effects. Overdose:** See SmPC for treatment guidance. **Licence Number:** PL 12064/0047. **Marketing Authorisation Holder:** Aurum Pharmaceuticals Ltd, Bampton Road, Romford, RM3 8UG. **Basic NHS Price:** £15.41 **Legal Category:** POM. **Further information:** Martindale Pharma, Bampton Road, Romford, RM3 8UG. Tel: 01277266600. **Date of Preparation:** October 2020.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Martindale Pharma, an Ethypharm Group Company. Tel: 01277266600. e-mail: drugsafety.uk@ethypharm.com