Ballarat Health Services

DRUG GUIDELINE

AMIODARONE (Intravenous)

SCOPE (Area):	**FOR USE IN:**	Intensive Care Unit, Coronary Care Unit, ED, Theatre General wards **by MET Liaison Nurse** only
	EXCLUSIONS:	Paediatrics (seek Paediatrician advice) and General Wards
SCOPE (Staff):		Medical, Nursing and Pharmacy

BRAND NAMES
Cordarone X®.

PHARMACOLOGY AND PHARMACOKINETICS
Amiodarone is classified as a class III (potassium channel blocking) antiarrhythmic drug, but it has a number of other actions that can contribute to both its antiarrhythmic and proarrhythmic potential. It is a noncompetitive antiadrenergic (beta-blocking class II) drug and demonstrates some degree of sodium channel blocking (class I) and calcium channel blocking (class IV) activity. It has variable oral bioavailability (20% to 80%) and the half-life is usually about 40 days, but is highly variable and can exceed 100 days due to extensive tissue distribution. Amiodarone is primarily metabolised in the liver. Each amiodarone molecule contains 2 atoms of iodine and is a structural analogue to thyroxine.

INDICATIONS
- Treatment and prophylaxis of serious tachyarrhythmias, including ventricular arrhythmias, atrial tachyarrhythmias and supraventricular tachycardia (atrioventricular nodal re-entry or bypass tract-mediated).

CONTRAINDICATIONS
- **Second or third degree heart block (without pacemaker).**
- **Symptomatic bradycardia (without pacemaker).**
- **Sick sinus syndrome (without pacemaker).**
- **Circulatory collapse or severe arterial hypotension.**
- **Allergy to amiodarone or iodine.**

PRECAUTIONS
- **Electrolyte disturbances (e.g. hypokalaemia, hyperkalaemia, hypomagnesaemia, hypocalcaemia)** – increase the risk of arrhythmias, correct before starting treatment if possible.
- **Multiple drug interactions –** many can lead to serious adverse effects – See Drug Interactions.
- **QT interval prolongation and increased risk of torsades de pointes** - check that QT interval is less than 500 milliseconds before use, as amiodarone may increase risk of arrhythmia by prolonging the QT interval. Avoid use if risk factors for prolonged QT interval (including genetic abnormalities, electrolyte disturbances (as above), increasing age, female gender,

bradycardia, heart failure, coronary heart disease and some drugs) are irreversible or cannot be corrected before giving amiodarone.

- **Atropine resistant bradycardia** – can occur with excessive amiodarone dosing.
- **Thyroid dysfunction (including goitre or nodules)** – increases risk of hypothyroidism or hyperthyroidism.
- **Lung disease (particularly with reduced diffusion capacity)** – gives less reserve to cope with the pulmonary adverse effects of amiodarone.
- **Hepatic** - use with caution in impairment due to reduced metabolism and risk of accumulation and/or hepatotoxicity.
- **Elderly** – heart rate may decrease markedly, dose may need decreasing.
- **Uncompensated or severe heart failure** – may be worsened, although amiodarone is the least negatively inotropic antiarrhythmic agent and is usually well tolerated in heart failure.
- **Hypotension** – intravenous amiodarone can worsen hypotension.
- **Surgery** – notify Anaesthetist patient is receiving amiodarone, rare cases of adult acute respiratory distress syndrome have followed immediately following surgery.

PREGNANCY AND BREASTFEEDING

Seek specialist advice before prescribing, information may update regularly.

DRUG INTERACTIONS

Amiodarone has a very long half-life and it may take weeks to months before an interaction fully develops, similarly when it is stopped interactions may continue for weeks to months. This list does not consider drugs that only interact with oral amiodarone, check references before commencing. Amiodarone is substrate for cytochrome P450 3A4 (CYP3A4), CYP2C8 and p-glycoprotein, as well as an inhibitor of CYP2D6, CYP2C9, CYP2A6 and p-glycoprotein and as such has a vast number of interactions. Only those of most importance have explanatory notes – refer to listed references for further information.

Amiodarone can prolong the QT interval and is known to cause potentially fatal torsades de pointes (see Precautions), combination with the following drugs increases this risk, avoid where possible, especially where a known risk exists. The below information is from Credible Meds *QTDrugs List* (https://www.crediblemeds.org/).

Known torsades de pointes risk:

Anagrelide, arsenic trioxide, azithromycin, chloroquine, chlorpromazine, ciprofloxacin, cisapride, citalopram, clarithromycin, cocaine, disopyramide, domperidone, donepezil, droperidol, erythromycin, escitalopram, flecainide, fluconazole, haloperidol, levomepromazine, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine, pentamidine, procainamide, propofol, quinidine, sevoflurane, sotalol, vandetanib,

Possible/conditional torsades de pointes risk:

Alfuzosin, amantadine, amisulpride, amitriptyline, apomorphine, aripiprazole, asenapine, atazanavir, bortezomib, chloral hydrate, clomipramine, clozapine, crizotinib, dabrafenib, dasatinib, degarelix, dexmedetomidine, dextropropoxyphene, diphenhydramine, dolasetron, doxepin, eribulin, famotidine, fingolimod, fluoxetine, foscarnet, frusemide, galantamine, granisetron, hydrochlorothiazide, hydroxychloroquine, imipramine, indapamide, itraconazole, ivabradine, ketoconazole, lapatinib, leuprolide, lithium, loratadine, mefloquine, mifepristone, metoclopramide, metronidazole, mirabegron, moclobemide, mirtazapine, nilotinib, norfloxacin, nortriptyline, olanzapine, oxytocin, paliperidone, pantoprazole, paroxetine, pasireotide, pazopanib, posaconazole, promethazine, propranolol, quetiapine, quinine, rilpivirine, risperidone, ritonavir, roxithromycin, sertraline, solifenacin, sorafenib, sunitinib, tacrolimus, tamoxifen,

telaprivir, tetrabenazine, tolterodine, toremifene, tropisetron, vardenafil, vemurafenib, venlafaxine, voriconazole, ziprasidone.

Drugs to be avoided with amiodarone

- **Drugs that prolong the QT interval** – see above.
- **Agalsidase alfa and beta** – amiodarone may antagonise their effect.
- **Atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, saquinavir, tipranivir** – may inhibit metabolism of amiodarone, increasing its concentration and possibly increasing its toxicity; monitor amiodarone concentration and adjust dose as necessary (manufacturer contraindicates some combinations – check carefully).
- **Everolimus** – amiodarone increases concentration of everolimus, seek Specialist advice.
- **Fingolimod** – can increase arrhythmogenic properties of amiodarone.
- **Sofosbuvir** – increased risk of possibly fatal bradycardia with amiodarone, seek Specialist advice.
- **Topotecan** – amiodarone increase concentration of topotecan, seek Specialist advice.

Drugs to use cautiously with amiodarone

- **Warfarin** - amiodarone inhibits metabolism of warfarin, increasing its anticoagulant effect and risk of bleeding. Reduce warfarin dose by about one-quarter, monitor INR frequently and adjust dose further as necessary.
- **Drugs that slow cardiac conduction and decrease heart rate (diltiazem, verapamil, beta-blockers, digoxin)** –additive effect with amiodarone resulting in significant bradyarrhythmia, monitor clinically and with ECG.
- **Antiarrhythmics** - amiodarone has a proarrhythmic effect and combination with other antiarrhythmics increases the risk of arrhythmias, avoid combinations if possible.
- **Drugs that cause hypokalaemia** – low potassium increases the risk of torsades de pointes.
- **Drugs lowering blood pressure** - BP reduction may be increased by intravenous amiodarone.
- **Cyclosporin and tacrolimus** - amiodarone may increase the concentration and risk of toxicity, monitor levels and adverse effects closely. See above for tacrolimus and prolonged QT.
- **Dabigatran** - amiodarone increases dabigatran concentration and the risk of bleeding, reduce dabigatran dose to 150 mg once daily in VTE prevention, no adjustment required in AF.
- **Digoxin** – as well as the additive cardiac effects described above, amiodarone increases digoxin concentration and the risk of toxicity. Halve the digoxin dose, monitor digoxin concentration, watch for bradyarrhythmia and ECG changes.
- **Eplerenone** - amiodarone increases the concentration of eplerenone and the risk of adverse effects (e.g. hyperkalaemia). Limit eplerenone dose to 25 mg daily and monitor potassium.
- **Flecainide** - amiodarone increases flecainide concentration and risk of toxicity; avoid combination or reduce dose of flecainide by about half, monitor for adverse effects. See MIMS (https://www.mimsonline.com.au.acs.hcn.com.au//Search/Search.aspx?acc=36265) for further information.
- **Fusidic acid** - concentration of either drug may be increased, avoid combination.
- **Metoprolol** – as well as the additive cardiac effects for betablockers described above, amiodarone may also increase metoprolol's concentration. Consider using a low dose to start metoprolol treatment, and monitor carefully.
- **Phenytoin** - amiodarone increases phenytoin concentration and risk of toxicity; monitor phenytoin concentration and adverse effects. Phenytoin may decrease amiodarone concentration, possibly decreasing its efficacy; monitor clinical effect.
- **Statins** - amiodarone can increase the risk of myopathy or rhabdomyolysis with most statins. Pravastatin does not have this effect and should be used where possible. If simvastatin must be used, maximum daily dose is 20 mg.

Drugs that interact to a lesser degree with amiodarone – check listed references (drugs listed above with QT prolongation are not listed again even if there is another interaction):
Abiraterone, afatinib, alfentanil, apixaban, aprepitant, artesunate, atomoxetine, bisoprolol, boceprevir, bosentan, brentuximab vedotin, captopril, carbamazepine, carvedilol, celecoxib, chlorpheniramine, chlorpromazine, cimetidine, clobazam, clonazepam, clopidogrel, cobicistat, codeine, colchicine, corticosteroids, cyclophosphamide, dapoxetine, dapsone, darifenacin, deferasirox, dextromethorphan, diltiazem, doxorubicin, doxorubicin liposomal, duloxetine, efavirenz, enzalutamide, etravirine, felodipine, fluphenazine, fluvoxamine, fosaprepitant, gefitinib, gemfibrozil, glibenclamide, gliclazide, glimepiride, glipizide, grapefruit juice, hydrocodone, ibuprofen, imatinib, irbesartan, irinotecan, isoniazid, ivacaftor, ketamine, lacosamide, lignocaine, loperamide, losartan, meloxicam, mestranol, modafinil, nebivolol, nevirapine, orlistat, oxycodone, paclitaxel, perhexiline, phenobarbitone, piroxicam, pioglitazone, primaquine, primidone, prucalopride, rabeprazole, rifabutin, rifampicin, rifaximin, romidepsin, rosiglitazone, ruxolitinib, simeprevir, sirolimus, sofosbuvir, St. John's wort, sulfadiazine, sulfamethoxazole, tamoxifen, temsirolimus, teniposide, teriflonomide, theophylline, tibolone, ticagrelor, tocilizumab, tofacitinib, tolvaptan, tramadol, trimethoprim, venlafaxine, verapamil, verteporfin, vinblastine, vincristine, vortioxetine, zuclopenthixol.

DOSAGE AND ADMINISTRATION

Requires continuous ECG monitoring and the availability of resuscitation equipment.
For administration only

- **in Intensive Care Unit, Coronary Care Unit, ED or Theatre**
- **by MET or Code Blue**
- **loading dose on General Wards by MET Liaison Nurse on the order of a Registrar**

Administer preferably via central line where repeated doses or a continuous infusion is anticipated. Use of peripheral veins may be associated with significant thrombophlebitis – if unavoidable (e.g. overnight) a large bore (18 gauge) peripheral line, no more distal than the antecubital fossa, may be used for ideally less than 12 hours (maximum 24 hours). The back of the hand is NOT to be used. For these short term peripheral lines, the site must be checked hourly and the patient asked to report any pain/discomfort. Any signs of thrombophlebitis must be reported immediately to Medical Staff.

Correct electrolyte disturbances (particularly potassium and magnesium) before commencing amiodarone where possible.

Amiodarone must be diluted prior to use. Dilute with glucose 5% only – amiodarone is incompatible with sodium chloride.

Note: Many references recommend placing infusions in glass containers, using low absorption giving sets and replacing infusions 12 hourly. This is rarely done in practice anymore as a number of references have shown amiodarone stable for 24 hours in PVC bags. A plasticiser (DEHP) can leech out of PVC bags, and patients continuing amiodarone infusion beyond 24 hours require AVIVA non-PVC glucose 5% 500 mL bags (stocked in ICU and 2GP Coronary Care Unit drug cupboard), as well as the Smartsite low-sorbing set (Part number 10010454, stocked in ICU and 2GP).

IV injection (emergency administration, via CVC where possible):
Monitor clinical signs and ECG very closely. Can cause severe hypotension
Amiodarone 150-300 mg (3-6 mL from ONE to TWO ampoules) diluted to 20 mL with glucose 5%, given by IV injection over 1-2 minutes.
Total volume: 20 mL.

Maximum total dose (load, breakthrough plus maintenance) for 60 kg or more is 1200 mg over 24 hours, or if less than 60 kg 20 mg/kg over 24 hours.

IV infusion (loading dose, via CVC where possible – see above):

Weight less than 60 kg:

Amiodarone 5 mg/kg diluted to 100 mL with glucose 5%, administer by IV infusion over 20 minutes.

Withdraw same volume from glucose 5% minibag as volume of amiodarone to be added – see table below.

Total volume: 100 mL.

Infusion rate: 300 mL/hr. Use Alaris® LVP with Guardrails® and select 'amIODAROne LOAD - < 60 kg' in Critical Care Adult or Coronary Care Unit profile.

Weight 60 kg or greater:

Amiodarone 300 mg (6 mL from TWO ampoules) added to 100 mL glucose 5%, administer by IV infusion over 20 minutes.

Total volume: 106 mL.

Infusion rate: 318 mL/hr. Use Alaris® LVP with Guardrails® and select 'amIODAROne LOAD - >= 60 kg' in Critical Care Adult or Coronary Care Unit profile.

IV infusion (maintenance dose for 24 hours only, via CVC where possible – see above):

Weight less than 60 kg:

Amiodarone 10-15 mg/kg diluted to 500 mL with glucose 5%, administer by IV infusion over 24 hours.

Withdraw same volume from glucose 5% IV bag as volume of amiodarone to be added – see table below.

Total volume: 500 mL.

Infusion rate: 20.8 mL/hr. Use Alaris® LVP with Guardrails® and select 'amIODAROne – MAINT < 60 kg' in Critical Care Adult or Coronary Care Unit profile.

Weight 60 kg or greater:

Amiodarone 900 mg (18 mL from SIX ampoules) added to 500 mL glucose 5%, administer by IV infusion over 24 hours.

Total volume: 518 mL.

Infusion rate: 21.6 mL/hr. Use Alaris® LVP with Guardrails® and select 'amIODAROne – MAINT >= 60 kg' in Critical Care Adult or Coronary Care Unit profile.

Amiodarone calculation table if weight less than 60 kg			
Weight	**Amiodarone loading dose (5 mg/kg). Diluted to 100 mL with glucose 5%. Administer over 20 mins at 300 mL/hr.**	**Amiodarone maintenance dose (10-15 mg/kg). Diluted to 500 mL with glucose 5%. Administer over 24 hours at 20.8 mL/hr.**	**Amiodarone breakthrough# dose (2 mg/kg). Administer from maintenance infusion using bolus function over 20 mins.**
40 kg	200 mg (4 mL*)	400-600 mg (8-12 mL*)	80 mg
45 kg	225 mg (4.5 mL*)	450-675 mg (9-13.5 mL*)	90 mg
50 kg	250 mg (5 mL*)	500-750 mg (10-15 mL*)	100 mg
55 kg	275 mg (5.5 mL*)	550-825 mg (11-16.5 mL*)	110 mg

*volume of amiodarone from ampoules to be added #see next page

Where required, commence oral/nasogastric amiodarone once the 24 hour maintenance infusion has finished. For patients unable to take oral/nasogastric medication, continue IV amiodarone at a reduced dose 300 mg added to 500 mL glucose 5% (total volume 506 mL) over 24 hours (21.1 mL/hr). Use Alaris® LVP with Guardrails® and select 'amIODAROne MAINT – Nil oral low dose' in Critical Care Adult or Coronary Care Unit profile. Note that patients requiring amiodarone infusion beyond 24 hours require AVIVA non-PVC glucose 5% 500 mL bags (stocked in ICU and 2GP Coronary Care Unit drug cupboard) as well as the Smartsite low-sorbing set (Part number 10010454, stocked in ICU and 2GP).

IV infusion (breakthrough arrhythmias during maintenance infusion, via CVC):

A breakthrough dose is occasionally given in ICU patients, and if prescribed is to be administered from the maintenance infusion using the bolus function to avoid exceeding the daily maximum limit. This bolus is set up in the Guardrails maintenance infusions – once infusion is running press 'Channel Select' on the amiodarone channel, then select 'Bolus'. Enter the dose as 2 mg/kg using the above table (>= 60 kg is preset at 120 mg), and run over 20 minutes. **Manually enter data, do not use the rapid bolus button.**

Weight less than 60 kg:

Amiodarone 2 mg/kg (from maintenance infusion), administer by IV infusion **over 20 minutes**.
Use Alaris® LVP with Guardrails® and select bolus function in 'amIODAROne MAINT - < 60 kg' in Critical Care Adult or Coronary Care Unit profile. Ensure correct dose and time are entered – **see table above**.

Weight 60 kg or greater:

Amiodarone 120 mg (69 mL from maintenance infusion), administered by IV infusion over 20 minutes.
Infusion rate: 207 mL/hr. Use Alaris® LVP with Guardrails® and select bolus function in 'amIODAROne MAINT - >= 60 kg' in Critical Care Adult or Coronary Care Unit profile.

General Administration Information

- **Infusion preparation:**
  Mix infusion thoroughly after adding amiodarone to avoid inadvertently giving a more concentrated dose.
  Infusion stable for 24 hours.
- **Infusion pump:** Alaris® LVP with Guardrails®.
- **Routes of administration:**
  IV injection: Yes, emergency use
  IV intermittent infusion (15-60 minutes): Yes
  IV continuous infusion: Yes
  IM injection: No
  Subcut injection: No
- **Compatible/incompatible IV drugs/fluids:**
  Only compatible with glucose 5%.
  Consult the Australian Injectable Drugs Handbook ('Yellow book') in your ward area. **Assume all unlisted drugs and IV fluids are incompatible – contact Pharmacy for further advice.**

MONITORING (INCLUDING BLOOD TESTS)

- Ensure QT interval less than 500 milliseconds prior to administration (See Precautions).
- Baseline 12 lead ECG, blood pressure, heart rate and rhythm, electrolytes (especially potassium and magnesium), lung function (including chest Xray), liver functions tests and thyroid function tests before starting treatment. Amiodarone can affect thyroxine's metabolism, and Pathology need to be aware when thyroid function tests are ordered if the patient is receiving amiodarone.

- Onset of effort dyspnoea or nonproductive cough may indicate interstitial pneumonitis (very rare). Perform a chest X-ray if suspected or annually.

NURSING PRACTICE POINTS

- Requires continuous ECG monitoring.
- Peripheral administration requires observation of the IV site at least hourly, and the patient must be instructed to report any pain/discomfort. Any signs of thrombophlebitis must be reported immediately to Medical Staff.
- Take baseline 12 lead ECG, blood pressure, heart rate and rhythm. Monitor blood pressure and heart rate every 5 minutes during the loading dose, then hourly during the maintenance infusion. Any signs of bradycardia or hypotension should be promptly reported to the Medical Officer.
- Monitor for prolongation of the QT interval.
- Ampoules with precipitate or cloudiness are not to be used. Solution is a clear, pale yellow.
- All injections and infusions are to be labelled as per CPP0022 Labelling of Injectable Medicines and Lines.

ADVERSE EFFECTS

Amiodarone has serious adverse effects (including the potential to worsen arrhythmias) and these are slow to resolve after it is stopped due to the very long half-life. This includes photosensitivity, and patients need to be warned to take sun protection measures even in the months following cessation of amiodarone.

Many of the adverse effects are related to dose and duration of treatment and may not appear for weeks, months or even years. Adverse reactions from the AMH are listed, see MIMS (https://www.mimsonline.com.au.acs.hcn.com.au//Search/Search.aspx?acc=36265) for a more complete list.

- **Common** - nausea and vomiting (especially while loading), hypotension (IV infusion), constipation, anorexia, taste disturbance (metallic taste, loss of taste), transient elevation of hepatic aminotransferases, thyroid dysfunction (see below), fever, photosensitivity, skin pigmentation (blue-grey), benign corneal microdeposits (see below), headache, dizziness, fatigue, neurotoxicity (tremor, ataxia, paraesthesia, peripheral neuropathy, limb weakness), sleep disturbances (vivid dreams or nightmares), pulmonary toxicity (see below) and moderate bradycardia.
- **Infrequent** - atrioventricular block, arrhythmias (new or exacerbated), phlebitis (with peripheral administration) and epididymitis.
- **Rare** – hepatotoxicity (may be fatal), optic neuropathy (see below), bronchospasm, alveolar haemorrhage, heart failure, acute respiratory distress syndrome, heart failure, torsades de pointes, severe bradycardia, thrombocytopenia, alopecia and allergic rash, SIADH.
- **Pulmonary toxicity** - two main types: an acute inflammatory disorder which can develop early or late, is reversible if drug withdrawn early and may respond to corticosteroids; and a chronic fibrotic form associated with prolonged exposure which is less reversible.
- **Thyroid dysfunction** - Hypothyroidism occurs mainly within the first 2 years and is more common in patients with thyroid disease. Thyrotoxicosis can occur, even months after stopping amiodarone. Iodine-induced thyrotoxicosis is more common in patients with thyroid disease. A destructive thyroiditis can also occur. Seek Cardiologist advice.
- **Ocular effects** - Reversible benign corneal microdeposits occur in most patients but rarely affect vision (photophobia, visual haloes may occur). Stop amiodarone if optic neuropathy or neuritis occurs.

DRUG PRESENTATIONS AND STORAGE

Amiodarone 150 mg/3 mL ampoules.

Store below 25°C. Do not refrigerate. Protect ampoules from light.
