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® and Amiodarone GH.

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 (22% to 86%) which is increased with food, and the elimination 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).**
- **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.
- **Severe hypotension** – intravenous amiodarone can worsen hypotension, this occurs more at faster rates and is likely due to the solubilisers polysorbate-80 and benzyl alcohol.
- Potential severe complications may occur in some patients taking amiodarone who undergo general anaesthesia, including bradycardia unresponsive to atropine, hypotension, conduction disturbances, and decreased cardiac output.

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 amiodarone is ceased interactions may continue for weeks to months. Amiodarone and its metabolites inhibit CYP2C9, CYP2D6, CYP3A4 and P-glycoprotein (P-gp) and may increase the concentrations of medications that are substrates of these pathways, possibly leading to toxicity. Amiodarone is also a substrate for cytochrome P450 3A4 (CYP3A4), CYP2C8 and p-glycoprotein.

Only medications interacting with amiodarone with a potential high severity are listed below given the vast number of interactions via multiple pathways. Interactions to amiodarone update regularly, it is recommended to check the relevant references below whenever prescribing amiodarone to check for any interacting medications or contact your clinical Pharmacist for advice.

References for current drug interaction information are:

- AMH individual monographs and drug interaction section, including CYP enzyme tables and p–glycoprotein table at https://amhonline.amh.net.au.acs.hcn.com.au/interactions.
- UpToDate Drug Interactions at https://www.uptodate.com/drug-interactions.
- University of Liverpool HIV drug interactions at https://www.hiv-druginteractions.org.
- Regarding QT prolonging medications - https://www.crediblemeds.org/ (free resource can be accessed by creating a login, also available as an App)

QT prolongation and torsades de pointes risk

Amiodarone can prolong the QT interval and is known to cause potentially fatal torsades de pointes (see Precautions). This risk increased with co-administered with other medications that also prolong the QT interval.

When prescribing amiodarone, review other co-prescribed on the Credible Meds® *QTDrugs List* as noted in box above. Ensure electrolytes are optimised, and consider ceasing other QT prolonging medications if not required.

Medication groups to be used with caution together with amiodarone:

- **Medications that prolong the QT interval** – see box above for more information.
- **Medications that slow cardiac conduction, decreasing heart rate (e.g. diltiazem, verapamil, beta-blockers, digoxin) -** administration with amiodarone may result in significant bradyarrhythmia, monitor clinically and with ECG.
- **Antiarrhythmic medications** – amiodarone is proarrhythmic and may increase the risk of arrhythmias if used with other antiarrhythmics, avoid combinations if possible.
- **Medications that may cause electrolyte abnormalities** – may increase the risk of arrhythmias and prolonging the QT interval – see Precautions.
- **Medications affected through CYP or P-gp as noted above** – these update regularly, see AMH or UpToDate drug interactions for current information.

Specific medications to be avoided with amiodarone if possible – check references:

- **Medications with concentrations increased by amiodarone with risk of toxicity –** docetaxel, doxorubicin, flecainide, paclitaxel, pazopanib.
- **Medications that may increase amiodarone concentrations and risk of toxicity –** grapefruit juice, sodium fusidate.
- **Agalsidase alfa (and to a lesser degree 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. Check University of Liverpool HIV drug interactions reference.
- **Sofosbuvir** (may be more severe if combined with daclatasvir) – may increase the risk of serious bradycardia with amiodarone. Avoid combination, however, if this is impossible, inpatient cardiac monitoring for the first 48 hours is recommended, then monitor daily for at least the next 2 weeks.

Medications with narrow therapeutic windows potentially requiring dose reduction or medication level monitoring when used with amiodarone – check references:

- Ciclosporin, dabigatran, digoxin, phenytoin, tacrolimus, warfarin.

Medications with reduced maximum doses, or alternative medications may be required when used with amiodarone – check references:

- Dabigatran (depending on indication), eplerenone, simvastatin.

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. When administered via a peripheral vein the risk of phlebitis increases with the dose and duration of the infusion, infusion site reactions are common and include severe pain, phlebitis and necrosis. 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.

See next page for dose table.

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.

See next page for dose table.

IV infusion maintenance dose over 24 hours (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 below

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. 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**. **Manually enter data, do not use the rapid bolus button.**

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. **Manually enter data, do not use the rapid bolus button.**

TOTAL LOADING DOSE REQUIRED AND OPTIONS AFTER COMPLETION OF FIRST 24 HOUR BAG OF AMIODARONE

Total loading dose:

Amiodarone has an extremely long half-life, and to achieve a total load (if amiodarone is continuing long term) may take days to weeks with a maximum dose of 1200 mg in 24 hours, and usually a tapering to the maintenance dose. Intravenous and enteral/PO dosing (see more below, including bioavailability) all contribute to the total load, and the following estimates may be taken into account:

- Generally a total load of 5-7 g of amiodarone for tachycardia in the context of atrial fibrillation or SVT is considered effective (maximum 1200 mg per 24 hours).
- Generally a total load of 8-10 g for ventricular tachyarrhythmia is considered effective (maximum 1200 mg per 24 hours).

Note: Whilst infusions above are named 'load' and 'maintenance', in reality the patient is still loading until these above amounts are reached, and their dose has reduced to a daily PO/enteral maintenance dose of 100-200 mg (or rarely 400 mg in ventricular arrhythmias).

Options after completion of first 24 hour bag of amiodarone:

Arrhythmia type and cause, response to amiodarone and overall clinical situation will determine the outcome after the first 24 hour bag. Possibilities include:

- Early reversion OR reaction to amiodarone and bag ceased partway through, or at the end of first bag and no further dosing is required.
- No or poor response to first bag and further 24 hour bag/s are required.
- Adequate response and dose switched to PO/enteral to continue loading until switched to maintenance dosing. See below for more information.
- Adequate response but patient unable to have PO/enteral ongoing dosing, so to continue on lower dose intravenous over 24 hours. An option of amiodarone 300 mg added to 500 mL glucose 5% (total volume 506 mL) over 24 hours (21.1 mL/hr) is available in Guardrails®. 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) as well as the Smartsite low-sorbing set (Part number 10010454, stocked in ICU).

Intravenous to PO/enteral switch

- Only required for patients continuing amiodarone therapy.
- Oral bioavailability is highly variable (22-86%), but is increased with food – administer all doses with meals where possible. Absorption may be significantly reduced with nasogastric administration compared to oral administration – consider switching/continuing intravenous if required in the clinical context of patient.
- Initial PO dose will be determined by the already received total amiodarone dose vs planned total load, arrhythmia type and clinical context of the patient. Oral loading usually commences at 200 mg tds (maximum 400 mg tds in ventricular tachyarrhythmia = 8.4 g in one week) with review to decrease the dose within one week.
- **AFTER COMPLETING THE TOTAL LOAD, THE ONGOING MAINTENANCE DOSE OF AMIODARONE IS USUALLY 100-200 MG PO DAILY (UNLESS ADVISED OTHERWISE BY AN ELECTROPHYSIOLOGIST). IF THIS DOSE RANGE HAS NOT BEEN ACHIEVED BY DISCHARGE, A PLAN TO REDUCE TO THIS MUST BE DOCUMENTED ON THE DISCHARGE SCRIPT, WITH NO LONGER THAN ONE WEEK BETWEEN DOSE REDUCTIONS.**

General Administration Information

- **Infusion preparation:**
  Mix infusion thoroughly after adding amiodarone to avoid inadvertently giving a more concentrated dose.
  Infusion stable for 24 hours. *Note that patients requiring amiodarone infusion beyond 24 hours require AVIVA non-PVC glucose 5% 500 mL bags (stocked in ICU) as well as the Smartsite low-sorbing set (Part number 10010454, stocked in ICU).*
- **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) for a more complete list if required. For advice regarding management refer to senior Medical staff or Pharmacists:

- **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.
- **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 (Cordarone X®) or freeze (GH brand). Protect ampoules from light.
