INDICATION

Amiodarone is an antiarrhythmic medication used to treat and prevent some types of irregular heartbeat. It should be initiated and monitored carefully only under specialist supervision.

Oral Amiodarone is indicated only for the following, when other treatments cannot be used:

- Severe rhythm disorders not responding to other therapies
- Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome.
- Atrial flutter and fibrillation
- All types of tachyarrhythmias of paroxysmal nature including: supraventricular, nodal and ventricular tachycardias, and ventricular fibrillation

When used by mouth, it can take a few weeks for effects to begin and as amiodarone has a long half-life; there is potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped.

Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system. Patients on long term treatment should be carefully supervised because these reactions may be delayed. The minimum effective maintenance dose should be given because undesirable effects are usually dose related.

GPs should review all patients that have been on amiodarone for longer than one-year to review the indication. GPs should have a low threshold and be encouraged to seek Cardiology advice if they have any doubts about the need to continue to prescribe amiodarone.

This shared care document covers use of oral amiodarone in the above indications in adults. Intravenous use, or use in paediatric patients is not covered by this guidance.

AREAS OF RESPONSIBILITY FOR SHARED CARE

Patients should be at the centre of any shared care arrangements. Individual patient information and a record of their preferences should accompany shared care prescribing guidelines, where appropriate.

Transfer of clinical responsibility to primary care should only be considered where the person’s clinical condition is stable or predictable.

Referral to the GP should only take place once the GP has agreed to this in each individual case, and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities.

The GP should confirm the agreement and acceptance of the shared care prescribing arrangement and that supply arrangements have been finalised. The secondary/tertiary provider must supply an adequate amount of the medication to cover the transition period. The patient should then be informed to obtain further prescriptions from the GP.

When clinical responsibility for prescribing is transferred to general practice, it is important that the GP, or other primary care prescriber, is confident to prescribe the necessary medicines. Shared care agreements play a key role in enabling primary care prescribers to prescribe medicines with which they may not initially be familiar.

Clinical responsibility for prescribing is held by the person signing the prescription, who must also ensure adequate monitoring.
**REFERRAL AND INITIATION**

Shared Care is only appropriate if it provides the optimum solution for the patient.

<table>
<thead>
<tr>
<th>Specialist Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> To assess the suitability of the patient for treatment with amiodarone, ensuring it is in line with the local and national recommendations.</td>
</tr>
<tr>
<td><strong>2</strong> Determine a management strategy and ensure follow-up in conjunction with the GP.</td>
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<tr>
<td><strong>3</strong> Where appropriate:</td>
</tr>
<tr>
<td>• Carry out baseline monitoring of the patient before commencing treatment with amiodarone, as a minimum:</td>
</tr>
<tr>
<td>o Urea and electrolytes</td>
</tr>
<tr>
<td>o liver function (particularly transaminases) before treatment</td>
</tr>
<tr>
<td>o thyroid (including ultrasensitive TSH)</td>
</tr>
<tr>
<td>o consideration given to a chest x-ray</td>
</tr>
<tr>
<td>• to initiate and stabilise the patient on treatment, providing at least 28 days’ treatment;</td>
</tr>
<tr>
<td>• assess response to first month’s treatment;</td>
</tr>
<tr>
<td>• obtain consent from the patient’s GP to continue prescribing once treatment has been stabilised; the consultant will seek an agreement with the GP prior to agreeing a treatment plan with the patient;</td>
</tr>
<tr>
<td>• continue to monitor the patient and their therapy at appropriate intervals in conjunction with the GP;</td>
</tr>
<tr>
<td>• ensure therapy has a specified stop or review date and date agreed with the GP and the patient where applicable.</td>
</tr>
<tr>
<td><strong>4</strong> To explain the possible side effects of the medication to the patient and emphasise the importance of regular monitoring, where required (refer to section below on adverse effects)</td>
</tr>
<tr>
<td><strong>5</strong> Ensure that patients know what to do and who to contact if they experience adverse events or an exacerbation of their condition.</td>
</tr>
<tr>
<td><strong>6</strong> To provide the GP with appropriate prescribing information and any additional information requested, and to offer telephone support.</td>
</tr>
<tr>
<td><strong>7</strong> To agree with the GP arrangements for any ongoing monitoring of the patient’s condition to ensure the safe use of amiodarone.</td>
</tr>
<tr>
<td><strong>8</strong> To be available for advice if the patient’s condition changes and to arrange follow up in clinic at intervals to monitor the progress of the disease and review the continued use of amiodarone.</td>
</tr>
<tr>
<td><strong>9</strong> To ensure that procedures are in place for the rapid re-referral of the patient by the GP.</td>
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<tr>
<td><strong>10</strong> To ensure the patient has given informed consent to their treatment.</td>
</tr>
<tr>
<td><strong>11</strong> To liaise with the GP on any suggested changes in prescribed therapy / notify GP of any changes in the patient’s condition as assessed on follow up.</td>
</tr>
<tr>
<td><strong>12</strong> To inform the GP when it is considered appropriate to discontinue treatment.</td>
</tr>
<tr>
<td><strong>13</strong> Report any adverse events, via <a href="https://yellowcard.mhra.gov.uk/">https://yellowcard.mhra.gov.uk/</a>.</td>
</tr>
</tbody>
</table>
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**General Practitioner Responsibilities**

1. Initially, to refer the patient to the cardiology specialist.
2. To prescribe amiodarone at the agreed dose after the initial 28-day period and monitor the patient’s ongoing response to amiodarone.
3. Carry out any agreed monitoring, which may include:
   - Urea and electrolytes, liver function (particularly transaminases), 6 monthly
   - Thyroid (including ultrasensitive TSH), 6 monthly during treatment and for several months following discontinuation
   - Chest x-ray if pulmonary toxicity suspected
   - Annual ophthalmological examination
4. Reporting the results of monitoring to the specialist if appropriate.
5. To deal with general health issues of the patient.
6. To liaise with the consultant regarding any complications or adverse effects of treatment.
7. To consider any side-effects reported by the patient and to discuss with the consultant if necessary.
8. To avoid or appropriately manage the drug interactions as listed below and in the current BNF.
9. Ensure that therapy has a specified stop or review date agreed with the specialist and the patient where applicable.

**Patient’s role (or that of carer)**

1. Report to the specialist or GP if he/she does not have a clear understanding of the treatment.
2. To be aware of when the treatment should be reviewed and or discontinued
3. Attend appropriate consultant and GP appointments.
4. Share any concerns or adverse effects in relation to treatment with amiodarone with their GP or consultant, particularly:
   - Shortness of breath or cough
   - Deterioration in general health (fatigue, weight loss and fever)
   - Visual disturbance
   - Pregnancy or suspected pregnancy

**SUPPORTING INFORMATION**

**Licensed indications & therapeutic class**

Oral Amiodarone is indicated only for the following, when other treatments cannot be used:

- Severe rhythm disorders not responding to other therapies
- Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome.
- Atrial flutter and fibrillation
- All types of tachyarrhythmias of paroxysmal nature including: supraventricular, nodal and ventricular tachycardias, and ventricular fibrillation
Dorset Medicines Advisory Group

Dose, route of administration and duration of treatment

A high dose is needed initially in order to achieve adequate tissue levels rapidly.

Treatment should be started with 200 mg, three times a day and may be continued for 1 week. The dosage should then be reduced to 200 mg, twice daily for a further week. After the initial period the dosage should be reduced to 200 mg daily, or less if appropriate.

Occasionally patients will be started on a higher loading dose of 400mg or 600mg three times a day for 1 week and then reduced to 200mg daily, this should only be initiated by a cardiology consultant.

The scored 100 mg tablet should be used to titrate the minimum dosage required to maintain control of the arrhythmia. The maintenance dose should be regularly reviewed, especially where this exceeds 200 mg daily.

It is particularly important that the minimum effective dose be used. In all cases the patient's management must be judged on the individual response and well-being.

Adverse effects (incidence, identification, importance and management)

<table>
<thead>
<tr>
<th>Common (between 1 in 10 and 1 in 100) or very common (&gt;1 in 10)</th>
<th>Arrhythmias; hepatic disorders; hyperthyroidism; nausea; respiratory disorders; skin reactions; constipation; corneal deposits; hypothyroidism; movement disorders; photosensitivity reaction; sleep disorders; taste altered; vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon (between 1 in 100 and 1 in 1,000)</td>
<td>Cardiac conduction disorders; dry mouth; myopathy (usually reversible on discontinuation); peripheral neuropathy (usually reversible on discontinuation)</td>
</tr>
<tr>
<td>Rare (between 1 in 1,000 and 1 in 10,000) or very rare (&lt;1 in 10,000)</td>
<td>Bronchospasm (in patients with severe respiratory failure); headache; idiopathic intracranial hypertension; nerve disorders; SIADH; alopecia; aplastic anaemia; epididymo-orchitis; erectile dysfunction; haemolytic anaemia; pulmonary haemorrhage; thrombocytopenia; vertigo</td>
</tr>
<tr>
<td>Frequency not known</td>
<td>Angioedema; confusion; delirium; pancreatitis; severe cutaneous adverse reactions (SCARs); altered smell sensation; appetite decreased; parkinsonism; vasculitis</td>
</tr>
</tbody>
</table>

Further information about adverse effects

- **Corneal microdeposits** – patients taking amiodarone may develop corneal microdeposits (reversible on withdrawal of treatment). If vision is impaired or if optic neuritis or optic neuropathy occur, amiodarone must be stopped to prevent blindness and expert advice sought.

- **Thyroid function** – amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism can occur. Hypothyroidism can be treated with replacement therapy without withdrawing amiodarone if it is essential; careful supervision is required.

- **Hepatotoxicity** – amiodarone is also associated with hepatotoxicity and treatment should be discontinued if severe liver function abnormalities or clinical signs of liver disease develop.
• **Pulmonary toxicity** – pneumonitis should always be suspected if new or progressive shortness of breath or cough develops in a patient taking amiodarone.

**Cautions and contra-indications**

**Cautions**

- Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system. Because these reactions may be delayed, patients on long-term treatment should be carefully supervised.

- Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances, amiodarone treatment should be withdrawn. If necessary beta-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.

- Oral amiodarone is not contra-indicated in patients with latent or manifest heart failure but caution should be exercised as, occasionally, existing heart failure may be worsened. In such cases, amiodarone may be used with other appropriate therapies.

- 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.

- Treatment should be discontinued in case of onset of 2nd or 3rd degree A-V block, sino-atrial block, or bifascicular block.

- Amiodarone has a low pro-arrhythmic effect. Onsets of new arrhythmias or worsening of treated arrhythmias have been reported. It is important, but difficult, to differentiate a lack of efficacy of the drug from a proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition.

- Amiodarone may increase the defibrillation threshold and/or pacing threshold in patients with an implantable cardioverter defibrillator or a pacemaker, which may adversely affect the efficacy of the device. Regular tests are recommended to ensure the proper function of the device after initiation of treatment or change in posology.

- Amiodarone may induce hypothyroidism or hyperthyroidism, particularly in patients with a personal history of thyroid disorders. Euthyroidism is usually obtained within 3 months following the discontinuation of treatment. Hypothyroidism can be treated with replacement therapy without withdrawing amiodarone if it is essential.

- In the case of hyperthyroidism, therapy should be withdrawn. Clinical recovery usually occurs within a few months, although severe cases have been reported. Courses of anti-thyroid drugs have been used for the treatment of severe thyroid hyperactivity; large doses may be required initially. Concomitant high dose corticosteroid therapy (e.g. 1 mg/kg prednisolone) may be required for several weeks.

- Elderly patients may be more susceptible to bradycardia and conduction defects if too high a dose is employed.

- Following drug withdrawal, residual tissue bound amiodarone may protect the patient for up to a month. However, the likelihood of recurrence of arrhythmia during this period should be considered.
If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed. Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness.

Amiodarone may be associated with a variety of hepatic effects, including cirrhosis, hepatitis, jaundice and hepatic failure. At the beginning of therapy, elevation of serum transaminases which can be in isolation (1.5 to 3 times normal) may occur. These may return to normal with dose reduction, or sometimes spontaneously. Isolated cases of acute liver disorders with elevated serum transaminases and/or jaundice may occur; in such cases treatment should be discontinued.

There have been reports of chronic liver disease. Alteration of laboratory tests which may be minimal (transaminases elevated 1.5 to 5 times normal) or clinical signs (possible hepatomegaly) during treatment for longer than 6 months should suggest this diagnosis. Abnormal clinical and laboratory test results usually regress upon cessation of treatment.

Amiodarone may induce peripheral sensorimotor neuropathy and/or myopathy. Both these conditions may be severe, although recovery usually occurs within several months after amiodarone withdrawal, but may sometimes be incomplete.

Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity (hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonitis. Presenting features can include dyspnoea (which may be severe and unexplained by the current cardiac status), non-productive cough and deterioration in general health (fatigue, weight loss and fever). Whilst the majority of cases have been reported with long term therapy, a few have occurred soon after starting treatment.

Patients should be instructed to avoid exposure to sun and to use protective measures during therapy as patients taking amiodarone can become unduly sensitive to sunlight, which may persist after several months of discontinuation of Amiodarone. In most cases symptoms are limited to tingling, burning and erythema of sun-exposed skin but severe phototoxic reactions with blistering may be seen.

Life-threatening or even fatal cutaneous reactions Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN). If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present amiodarone treatment should be discontinued immediately.

**Contraindications**

- Sinus bradycardia and sino-atrial heart block. In patients with severe conduction disturbances (high grade AV block, bifascicular or trifascicular block) or sinus node disease, amiodarone should be used only in conjunction with a pacemaker.
- Evidence or history of thyroid dysfunction. Thyroid function tests should be performed in all patients prior to therapy.
- Known hypersensitivity to iodine or to amiodarone, or to any of the excipients. (One 200 mg tablet contains approximately 75 mg iodine).
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- The combination of amiodarone with drugs which may induce torsades de pointes is contraindicated
- Pregnancy - in view of its effect on the foetal thyroid gland, amiodarone is contraindicated during pregnancy except in exceptional circumstances.
Amiodarone is excreted into the breast milk in significant quantities and breast-feeding is contra-indicated.

**Monitoring requirements and responsibilities**

- Clinical and biological thyroid monitoring (including ultrasensitive TSH) should be performed prior to therapy in all patients. Monitoring should be carried out during treatment, at six-monthly intervals, and for several months following its discontinuation. This is particularly important in the elderly.
- Unless blurred or decreased vision occurs, ophthalmological examination is recommended annually.
- It is advisable to monitor liver function particularly transaminases before treatment and six monthly thereafter. Amiodarone dose should be reduced or the treatment discontinued if the transaminase increase exceeds three times the normal range.
- Patients should be carefully evaluated clinically and consideration given to chest X-rays before starting therapy. During treatment, if pulmonary toxicity is suspected, this should be repeated and associated with lung function testing including, where possible, measurement of transfer factor.

**Clinically important drug interactions and their management**

Concomitant use of amiodarone is **not recommended** with the following drugs:

- beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem), potentiation of negative chronotropic properties and conduction slowing effects may occur
- stimulant laxative agents which may cause hypokalaemia
- sofosbuvir in combination with another HCV direct acting antiviral (such as daclatasvir, simeprevir, or ledipasvir) – may lead to serious symptomatic bradycardia. Refer to MHRA advice for more information.
- Combined therapy with the following drugs which prolong the QT interval is contra-indicated due to the increased risk of torsades de pointes; for example:
  - Class Ia anti-arrhythmic drugs e.g. quinidine, procainamide, disopyramide
  - Class III anti-arrhythmic drugs e.g. sotalol,
  - intravenous erythromycin, co-trimoxazole or pentamidine injection
  - some anti-psychotics e.g. chlorpromazine, fluphenazine, pimozide, haloperidol, amisulpiride and
  - lithium and tricyclic anti-depressants e.g. doxepin, amitriptyline
  - certain antihistamines e.g., mizolastine
  - anti-malarials e.g. quinine, mefloquine, chloroquine, halofantrine.
  - Moxifloxacin

**Other drug/food interactions**

- 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.
- Phenytoin: phenytoin dosage should be reduced if signs of overdosage appear (resulting in neurological signs)
Caution should be exercised over combined therapy with the following drugs which may also cause hypokalaemia and/or hypomagnesaemia, e.g. diuretics, systemic corticosteroids, tetracosactide, intravenous amphotericin.

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

Digitalis: administration of amiodarone to a patient already receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels. Clinical, ECG and biological monitoring is recommended and digoxin dosage should be halved.

Anticoagulants: caution should be exercised when amiodarone is co-administered with warfarin or dabigatran due to the risk of bleeding. For warfarin more frequent monitoring of prothrombin time both during and after treatment is recommended.

Plasma levels of ciclosporin may increase as much as 2-fold when used in combination with amiodarone. A reduction in the dose of ciclosporin may be necessary to maintain the plasma concentration within the therapeutic range.

Risk of muscular toxicity (e.g. rhabdomyolysis) is increased by concomitant administration of amiodarone with statins metabolised by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolised by CYP 3A4 when given with amiodarone.

Drugs metabolised by cytochrome P450 3A4: may increase risk of toxicity – examples of such drugs are lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine ergotamine and colchicine.

Co-administration of amiodarone with drugs known to prolong the QT interval (such as clarithromycin) must be based on a careful assessment of the potential risks and benefits for each patient since the risk of torsade de pointes may increase and patients should be monitored for QT prolongation.

Concomitant use of amiodarone with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contra-indicated). There have been rare reports of QTc interval prolongation, with or without torsades de pointes

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

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

Patient and carer advice

Because of the possibility of phototoxic reactions, patients should be advised to shield the skin from light during treatment and for several months after discontinuing amiodarone; a wide-spectrum sunscreen to protect against both long-wave ultraviolet and visible light should be used.

If taking amiodarone with concomitant sofosbuvir and daclatasvir, simeprevir and sofosbuvir, or sofosbuvir and ledipasvir, patients and their carers should be told how to recognise signs and symptoms of bradycardia and heart block and advised to seek immediate medical attention if symptoms such as shortness of breath, light-headedness, palpitations, fainting, unusual tiredness or chest pain develop.
Although there have been no literature reports on the potentiation of hepatic adverse effects of alcohol, patients should be advised to moderate their alcohol intake while taking amiodarone.

Patients should be advised to avoid grapefruit juice should be avoided during treatment with oral amiodarone.

Patients should be advised to share any concerns or adverse effects in relation to treatment with amiodarone with their GP or consultant, particularly:
  - Shortness of breath or cough
  - Deterioration in general health (fatigue, weight loss and fever).
  - Visual disturbance
  - Pregnancy or suspected pregnancy

Peer-reviewed references for product usage

2. BNF online via Medicines Complete (accessed 9/4/2019)

Refer to page 10 of NHS England’s guidance on Responsibility for prescribing between Primary & Secondary/Tertiary Care for more information/guidance about taking on prescribing of specialist medicines.

This list is not exhaustive. The manufacturer’s summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug costs (correct at April 2019)

<table>
<thead>
<tr>
<th>Strength</th>
<th>Packsize</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>100mg tablets</td>
<td>28</td>
<td>£1.63</td>
</tr>
<tr>
<td>200mg tablets</td>
<td>28</td>
<td>£3.01</td>
</tr>
</tbody>
</table>

Written By: Cardiology working group | June 2019
Approved By: Dorset Medicines Advisory Group | July 2019
Date of next review: July 2021 or before, in light of new evidence or information.