# National shared care protocol: Adapted for use as WYICS amber guidance.

# Amiodarone for patients within adult services

**Please ensure that Summaries of Product Characteristics (SPCs), British National Formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites are reviewed for up-to-date information on any medicine.**

## Specialist responsibilities

- Assess the patient and provide diagnosis; ensure that this diagnosis is communicated to patient's GP.
- Discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling (see section 11) to enable the patient to reach an informed decision. Obtain informed consent. Provide an appropriate patient information leaflet.
- Assess for contraindications and cautions (see section 4) and interactions (see section 7).
- Conduct required baseline investigations and initial monitoring (see section 8).
- Initiate and optimise treatment as outlined in section 5. Prescribe the maintenance treatment for a minimum of 4 weeks.
- Once treatment is optimised, send information to the patient's GP practice, detailing the diagnosis, current and ongoing dose, any relevant test results and when the next monitoring is required. Include contact information (section 13).
- Prescribe sufficient medication to enable transfer to primary care.
- Conduct the required reviews and monitoring in section 8 and communicate the results to primary care. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.
- Reassume prescribing responsibilities if a patient becomes or wishes to become pregnant.

- Provide advice to primary care on the management of adverse effects if required.

## Primary care responsibilities

- Respond to the specialist in writing within 2 weeks if unwilling to take over prescribing and monitoring as requested by specialist. Include rationale for unwilling to take over prescribing.
- If accepted, prescribe ongoing treatment as detailed in the specialist's request and as per section 5, taking into any account potential drug interactions in section 7.
- Adjust the dose of amiodarone prescribed as advised by the specialist.
- Conduct the required monitoring as outlined in section 9. Communicate any abnormal results to the specialist.
- Manage adverse effects as detailed in section 10 and discuss with specialist team when required.
- Stop amiodarone and make an urgent referral to the specialist if hyperthyroidism, thyrotoxicosis, new or worsening arrhythmia or heart block, ophthalmological effects, hepatotoxicity, pulmonary toxicity or bullous skin reactions are suspected.
- The half-life of amiodarone is very long, with an average of 50 days (range 20-100 days).
- Refer the management back to the specialist if the patient becomes or plans to become pregnant.
- Stop treatment as advised by the specialist.

## Patient and/or carer responsibilities

- To agree and accept responsibility for taking amiodarone as prescribed.
- To understand how to take amiodarone safely.
- To understand the duration of treatment prescribed initially by the hospital specialist.
- To understand the most common adverse events/side effects and inform the Specialist/GP as soon as reasonably possible should they occur and significantly affect the use of the medicines.
- To understand the circumstances under which the medicines should be immediately stopped and what action to take.
- To understand contents of written information provided by the Specialist and in the patient information leaflet supplied with the medicines and to seek clarification if required.
- To attend for blood tests/disease monitoring on time. Be aware that medicines may be stopped if they do not attend.

- To check with the community pharmacist that there are no interactions with amiodarone, and other medications taken including other prescribed medications, medicines bought over the counter and herbal/homoeopathic products.
- To check with dentists or other specialists who may prescribe medicines that there are no interactions with amiodarone.
- Avoid grapefruit juice while taking amiodarone and for several months after discontinuation
- Moderate their alcohol intake to no more than 14 units per week to reduce the risk of hepatotoxicity.
- To contact the GP, Specialist or Medicines Information patient helpline if further information or advice is needed about this medication or if there is anything they do not understand. More information on asking about medication can be found in the Me & My Medicines Charter https://meandmymedicines.org.uk/the-charter/
- Use an appropriate form of contraception, as agreed with their doctor/nurse/sexual health service.
- Inform the specialist or primary care prescriber immediately if they become pregnant or wish to become pregnant.
- The NHS Website – NHS information on health link and medicines link.

## 1. Background

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Amiodarone is used in the treatment of arrhythmias, as detailed in section 2. It has an important place in the treatment of severe cardiac rhythm disorders where other treatments either cannot be used or have failed. Amiodarone has potentially serious adverse effects and its use requires regular monitoring.

Due to the significant safety concerns, NHS England (NHSE) and NHS Clinical Commissioners' (NHSCC) guidance advises that prescribers should not initiate amiodarone in primary care for any new patients. In exceptional circumstances, if there is a clinical need for amiodarone to be prescribed, this must be initiated by a specialist and only continued under an amber guidance arrangement in line with NICE clinical guidance Atrial fibrillation: NG 196. NICE defines the place in therapy of amiodarone in NG196, and has made a "Do not do" recommendation: "**Do not offer amiodarone for long-term rate control**". Amiodarone may also be suitable in patients prior and post cardioversion or in specific patients who have heart failure or left ventricular impairment.

Where there is an existing cohort of patients taking amiodarone who do not meet the amber guidance requirements, it is recommended that these patients be reviewed to ensure that prescribing remains safe and appropriate.

## 2. Indications

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Licensed indications:

- Atrial flutter fibrillation / atrial fibrillation when other drugs cannot be used.
- All types of tachyarrhythmias of paroxysmal nature including: supraventricular, nodal and ventricular tachycardias and ventricular fibrillation when other drugs cannot be used.

## 3. Indications

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National scoping did not identify any additional appropriate off-label indications

## 4. Contraindications and cautions

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Please see BNF & SPC for comprehensive information.

## 5. Initiation and ongoing dose regimen

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- The patient will be followed up by cardiology until their condition is stable then their care will be transferred to the GP.
- The patient can be referred back to the hospital specialist for advice or review when necessary.
- The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.
- Termination of treatment will be the responsibility of the specialist.

**Initial stabilisation:**

200mg three times per day for one week, then reduce to 200mg twice per day for one week.

Amiodarone is initiated with a loading dose in order to achieve adequate tissue levels rapidly. Rarely, the specialist team may use an alternative loading regimen.

**The loading period must be prescribed by the initiating specialist.**

**Maintenance dose (following initial stabilisation):**

200mg per day, or less if appropriate. The minimum dose required to control the arrhythmia should be used.

Rarely, a higher maintenance dose may be required. The maintenance dose should be reviewed regularly, particularly if it exceeds 200mg per day.

**The initial maintenance dose must be prescribed by the initiating specialist.**

**See clinic referral letter for recommended dose for a particular patient**

**Conditions requiring dose adjustment:**

Although there is no evidence that dose requirements for elderly patients are lower, they may be more susceptible to bradycardia and conduction defects if too high a dose is prescribed. The minimum effective dose should be used. Particular attention should be paid to monitoring thyroid function.

## 6. Pharmaceutical aspects

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| Route of administration: | Oral |
| Formulation: | • Tablets; 100mg and 200mg |
| Administration details: | For oral administration.<br>Maintenance dose can be given once daily, however doses >200 mg daily (including loading period) may be given as split doses to minimise nausea.<br>If necessary, tablets may be crushed and dispersed in water, but have a bitter taste (unlicensed). Different brands may disperse in water at notably different rates. The solution for injection is irritant and should not be given orally. |
| Other important information: | The half-life of amiodarone is very long, with an average of 50 days (range 20-100 days). Side effects slowly disappear as tissue levels fall. 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. |

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| | Grapefruit juice should be avoided during treatment with oral amiodarone and for several months after discontinuation (see section 7). |

## 7. Significant medicine interactions

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The following list is not exhaustive. Please see BNF or SPC for comprehensive information and recommended management.

**Amiodarone is associated with a large number of interactions, some of which are significant enough to contraindicate concurrent use, require dose adjustment and/or additional monitoring (see section 4).**

Amiodarone is an enzyme inhibitor and can increase exposure to a number of medicines including:

- P-glycoprotein (PgP) substrates (e.g. digoxin, dabigatran)
- CYP2C9 substrates (e.g. warfarin, phenytoin)
- For patients already taking warfarin. Inform warfarin clinic immediately when amiodarone is started (or stopped) an INR check will be arranged within 7 days (maximum) of initiation. Further monitoring will be decided by the anticoagulant clinic depending on the result. The potentiation of warfarin starts within a few days and is usually maximal by 2 to 7 weeks. Dose reductions of 25-50% may be required. It is vital that the anticoagulant clinic is informed when amiodarone is commenced, and patients should also be encouraged to contact their warfarin clinic to inform them of the medication change. · Amiodarone should be used with caution with any drugs which cause prolonged QT interval or hypokalaemia.
- If amiodarone is being considered for a patient on warfarin then the prescriber should also consider switching warfarin to a DOAC if clinically acceptable (excluding patients with metallic valve replacements).
- CYP3A4 substrates (e.g. ciclosporin, statins, fentanyl, sildenafil, colchicine)
- CYP2D6 substrates (e.g. flecainide)

Amiodarone interacts with other medicines that:

- induce Torsade de Points or prolong QT (e.g. other anti-arrhythmics, antipsychotics, antidepressants, clarithromycin, erythromycin )
- lower heart rate (e.g. beta-blockers, calcium channel blockers)
- induce hypokalaemia (e.g. diuretics, stimulant laxatives)
- induce hypomagnesaemia (e.g. diuretics, systemic corticosteroids)

Other interactions include:

- CYP3A4 and CYP2C8 inhibitors: may increase exposure to amiodarone (e.g. cimetidine, letermovir, ritonavir, darunavir, grapefruit juice)
- Sofosbuvir with daclatasvir; sofosbuvir and ledipasvir; simeprevir with sofosbuvir: risk of severe bradycardia and heart block (mechanism unknown) see MHRA advice
- **Due to the long half-life of amiodarone, there is potential for drug interactions to occur for several weeks/months after treatment has been discontinued.** See SPC for information on managing interactions.

## 8. Baseline investigations, initial monitoring and ongoing monitoring to be undertaken by specialist

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Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in immediate future will prescribing and monitoring be transferred to primary care.

**Baseline investigations:**

- Thyroid function tests (free T4, and TSH)
- Liver function tests (LFTs, particularly transaminases)
- Urea and electrolytes (U&Es, including potassium)
- Electrocardiogram (ECG)
- Chest X-ray within the last 3-6 months
- For patients taking warfarin: monitor international normalised ratio (INR) at baseline and during dose stabilisation period.
  For patients already taking warfarin. Inform warfarin clinic immediately when amiodarone is started (or stopped) an INR check will be arranged within 7 days (maximum) of initiation. Further monitoring will be decided by the anticoagulant clinic depending on the result. The potentiation of warfarin starts within a few days and is usually maximal by 2 to 7 weeks. Dose reductions of 25-50% may be required. It is vital that the anticoagulant clinic is informed when amiodarone is commenced, and patients should also be encouraged to contact their warfarin clinic to inform them of the medication change. · Amiodarone should be used with caution with any drugs which cause prolonged QT interval or hypokalaemia.
- If amiodarone is being considered for a patient on warfarin, then the prescriber should also consider switching warfarin to a DOAC if clinically acceptable (excluding patients with metallic valve replacements).
- For patients taking digoxin: clinical monitoring is recommended, and the digoxin dose should be halved. Digoxin levels should be monitored appropriately.

**Disease monitoring:**

- ECG to be performed if a patient is noted to be bradycardic or presents with any other red flag symptoms such as syncope.
- Chest X-ray and pulmonary function tests, if respiratory symptoms or toxicity suspected

After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.

**Follow Up:**

The patient will be followed up by cardiology until their condition is stable then their care will be transferred to the GP. The patient can be referred back to the hospital specialist for advice or review when necessary.

## 9. Ongoing monitoring requirements to be undertaken by primary care

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See section 10 for further guidance on management of adverse effects/responding to monitoring results.

| Monitoring and advice | Frequency |
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| • Thyroid function tests (free T4 and TSH)<br>• LFTs (particularly transaminases)<br>• U&Es (including potassium) | Perform all tests every 6 months during treatment, and 6 months after discontinuation.<br>Thyroid function should continue to be monitored for up to 12 months after discontinuation, with frequency determined clinically. |
| • ECG | to be performed if a patient is noted to be bradycardic or presents with any other red flag symptoms such as syncope. |

**(If relevant) If monitoring results are forwarded to the specialist team, please include clear clinical information on the reason for sending, to inform action to be taken by secondary care.**

## 10. Adverse effects and other management

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**Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit** www.mhra.gov.uk/yellowcard

For information on incidence of ADRs see relevant summaries of product characteristics

| Result | Action for primary care |
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| **As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance.** | |
| **The most serious toxicity with amiodarone is seen with long-term use and patients may therefore present first to primary care. Due to the long half-life of amiodarone there is potential for adverse effects to occur for several weeks/months after treatment has been discontinued.** | |
| Electrolyte deficiency:<br>hypokalaemia / hypomagnesaemia | Continue amiodarone. Correct deficiency as per local guidelines. Review other medicines that may be contributing to a deficiency |
| **Cardiovascular effects:**<br>Bradycardia:<br>• Heart rate 50 - 60bpm without symptoms | Continue amiodarone. Repeat monitoring. No action required unless symptoms develop or heart rate decreases further. |
| • Heart rate ≤ 50bpm, or ≤ 60bpm with symptoms | Discuss with specialist team; dose reduction may be required |
| Worsening of arrhythmia, new arrhythmia, or heart block | **Stop amiodarone.** Urgent referral to initiating specialist. |
| **Thyroid dysfunction**: | |

| | Result | Action |
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| TSH normal | Normal (It is not unusual for patients on amiodarone to have slight elevations of TSH and T4). | Repeat every 6 months |
| TSH > 4.5 mU/l | TSH > 4.5 mU/l,<br>fT4 elevated and duration less than 3 months. | Observe<br>Repeat in 3 months |
| Sub clinical hypothyroidism | TSH > 10 mU/l,<br>fT4 normal | Consider treating with levothyroxine or repeat in 3 months |

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| | persisting for over 6 months | |
| Hypothyroid | TSH > 4.5 mU/l, fT4 low | May be treated with levothyroxine if amiodarone is considered essential |
| Thyrotoxicosis | TSH < 0.1 mU/l T4 normal or minimally increased | Repeat in 2-4 weeks |
| | TSH < 0.1 mU/l & T4 elevated or 50% greater than baseline | Seek specialist endocrine advice - urgently if patient symptomatic. May advise amiodarone withdrawal. Arrange TSH-receptor antibodies and TPO antibodies. |

**Note:** Amiodarone elevates free T4 and TSH levels and tends to lower T3 levels. The above changes are not pathological and merely confirm compliance with medication. (Source: AL3 guidance document, Leeds Health Pathways)

Only measure free (or at LTHT) total T3 levels if the TSH level was suppressed concern about the development of amiodarone induced thyrotoxicosis. Measuring T3 level in suspected cases of hypothyroidism (whatever the cause), is not helpful.

Patients on amiodarone frequently don't show clinical features of thyrotoxicosis and sometimes they present with tiredness and often weight loss.

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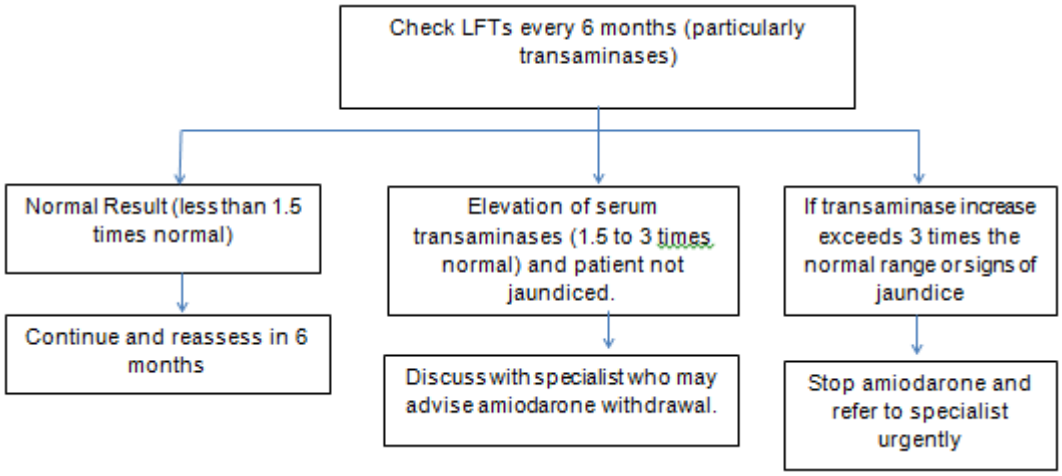
| **Ophthalmological effects:**<br>Optic neuropathy/neuritis;<br>blurred or decreased vision | **Stop amiodarone.** Urgent referral to initiating specialist and ophthalmology. |
| Corneal micro-deposits:<br>blueish halos when looking at bright lights, with no blurred or decreased vision | Continue amiodarone; reversible on discontinuation. The deposits are considered essentially benign and do not require discontinuation of amiodarone. |
| **GI disturbance**: nausea, anorexia, vomiting, taste disturbance | Continue amiodarone. May require dose reduction; discuss with specialist if persistent. |
| **Liver Function** | See flow diagram below |



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| **Neurological symptoms**:<br>Extrapyramidal tremor, ataxia, peripheral neuropathy, myopathy | Continue amiodarone. May require dose reduction; discuss with specialist. |
| **Pulmonary toxicity**: including pneumonitis or fibrosis<br>new/worsening cough, shortness of breath or deterioration in general health (e.g. fatigue, weight loss, fever) | **Stop amiodarone.** Urgent referral to initiating specialist and respiratory specialist. Admission may be required. |
| **Bullous skin reactions**:<br>life threatening or even fatal cutaneous reactions Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) | **Stop amiodarone.** Urgent referral to dermatology, inform initiating specialist. |
| Photosensitivity | Continue amiodarone. Reinforce appropriate self-care e.g. sun avoidance and purchasing of a broad spectrum sunscreen (at least SPF30). |
| Skin discolouration (blue/grey):<br>occurs in unprotected, light exposed skin | Continue amiodarone. May require dose reduction; discuss with specialist.<br>Reinforce self-care measures (as for photosensitivity above). Pigmentation slowly disappears following treatment discontinuation |

## 11. Advice to patients and carers

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The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.

**The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:**

- **Breathlessness, non-productive cough or deterioration in general health (e.g. fatigue, weight loss, fever)**
- **New or worsening visual disturbances**
- **Progressive skin rash +/- blisters or mucosal lesions**
- **Signs and symptoms of bradycardia or heart block,** e.g. dizziness, fatigue, fainting, shortness of breath, chest pain or palpitations, confusion or trouble concentrating

**The patient should be advised:**

- To use appropriate self-care against the possibility of phototoxic reactions: e.g. sun avoidance, protective clothing, avoiding tanning (including tanning beds) and to purchase and use a broad spectrum sunscreen (at least SPF30). These measures to be continued for the duration of therapy and for several months after discontinuation.
- If taking a statin and amiodarone, to report any signs of unexplained muscle pain, tenderness, weakness or dark coloured urine.
- Avoid grapefruit and grapefruit juice while taking amiodarone and for several months after discontinuation.
- Although there have been no case reports on enhanced hepatoxicity with alcohol, patients should be advised to moderate their alcohol intake to no more than 14 units per week while taking amiodarone.

Patient information:

**British Heart Foundation – anti-arrhythmics:**
https://www.bhf.org.uk/informationsupport/heart-matters-magazine/medical/drug-cabinet/anti-arrhythmics

## 12. Pregnancy, paternal exposure and breast feeding

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It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist.

**Pregnancy:**

Due to the risk of neonatal goitre, amiodarone should only be prescribed in pregnancy if there is no alternative. Under these circumstances prescribing and monitoring will be the responsibility of the initiating specialist.

**Breastfeeding:**

Amiodarone is excreted into the breast milk in significant quantities; breast feeding is considered contraindicated due to the potential risk of iodine-associated adverse effects in the infant.

- Information for healthcare professionals: https://www.sps.nhs.uk/medicines/amiodarone/

## 13. Specialist contact information

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See letter from specialist

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| Original RMOC document Version 1 | July 2022 |
| Date for review of original RMOC doc | January 2025 |
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| Date first draft adapted from RMOC guidance | 23rd January 2023 |
| Sent to PAG/APC members for comment | 20th February 2023 |
| Comments from APC members by | 31st March 2023 |
| Document updated after comments date of 2nd draft | 4th May 2023 |
| Date of 2nd draft | 11th May 2023 |
| 2nd draft circulated to APC members | 17th May 2023 |
| Comments from APC members by | 24th May 2023 |
| Date Ratified at APC subject to minor amendments | 24th May 2023 |
| Amendments made | 25th May 2023 |
| Final Version | 25th May 2023 |
| Review Date | 25th May 2026 |