Name of Shared Care Agreement:

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| **Amiodarone tablets (Adults)** |
| **Reference number:** |

Hepatitis C drug interactions added 18th August 2015 post MHRA advice & MAG approval. Original agreement signed June 2015 – Jacob George, Philip McLoughlin and Michelle Watts on behalf of MAG, ADTC & PCS.

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| Shared care agreement has been developed appropriately | Signed:<br><br>Jacob George<br><br>For Medicines Advisory Group<br>Date: June 2015 |
| Shared care agreement meets the governance requirements of NHS Tayside | Signed:<br><br>Philip McLoughlin<br><br>For Area Drug and Therapeutics Committee<br>Date: June 2015 |
| Protocol has been reviewed by Primary Care Services and remuneration for monitoring requirements by GPs (if any) has been negotiated | Signed:<br><br>Michelle Watts<br><br>For Primary Care services<br>Date: June 2015 |

Where there is a substantial shift in expenditure from hospital prescribing to GP/ nurse prescribing as a result of this shared care protocol, the clinical group must discuss budgetary implications with the CHP Heads of Pharmacy/ General Managers

# Shared Care Agreement: Oral amiodarone

*This document should be read in conjunction with the current Summary of Product Characteristics if available* http://www.medicines.org.uk/

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| **1. Therapeutic use & Background** | **Amiodarone** is used in the treatment of arrhythmias, particularly when other drugs are ineffective or contra-indicated. Oral amiodarone should be initiated only under hospital or specialist supervision. Amiodarone is a potentially toxic drug and the patient should be monitored for hypo or hyper thyroidism, hepatotoxicity, pulmonary toxicity, peripheral neuropathy & phototoxicity. It was felt that monitoring may be variable across NHS Tayside and that a shared care agreement should improve the safer use of this drug. |
| **2. Indications for therapy** | Amiodarone can be used for paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, and ventricular fibrillation. It can also be used for tachyarrhythmias associated with Wolff-Parknson-White syndrome. |
| **3. Typical Dosage Regimen** | **A loading regimen is necessary and will either be prescribed by the specialist centre or communicated to the GP to prescribe.**<br><br>**Usual loading dose:** 200mg three times daily for one week, then 200mg twice daily for one week, then a further reduction to 200mg daily.<br><br>**Maintenance:** 200mg daily, however 100mg daily may be sufficient in elderly patients. The minimum dose to control the arrhythmia is used. In rare cases a maintenance dose of above 200mg daily may be used. |
| **4. Administration** | Oral administration of tablets<br>Grapefruit juice should be avoided |
| **5. Annual cost of therapy** | £23.20<br><br>Price taken from: Scottish Drug Tariff, Sept 2014 |
| **6. Adverse effects, drug interactions and warnings** | **Adverse effects:**<br>**The most serious toxicity with amiodarone is seen with long-term use and patients may therefore present first to GPs.**<br><br>**Please refer to Summary of Product Characteristics for a full list of adverse effects at** http://www.medicines.org.uk<br><br>Many adverse effects are dose-related and reversible with reduction in dose; however, because of amiodarone's long half-life (average half life of 50 days) this can take some time and adverse effects may develop after treatment is stopped. |

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| | • **Gastro-Intestinal** - nausea, vomiting and taste disturbance.<br>• **Cardiovascular** - bradycardia (reduce dose or if severe withdraw treatment), conduction disturbances (withdraw treatment). Note amiodarone has a long half life so may require pacemaker, beta-adrenostimulants or glucagon – see SPC for further information<br>• **Endocrine disorders** - hypothyroidism (20% patients) and hyperthyroidism (5% of patients) occurs commonly and thyroid function should be carefully monitored. If the patient becomes hypothyroid amiodarone may be withdrawn if clinically acceptable in which case the hypothyroidism usually resolves within 12 months. However some patients may need treatment for their hypothyroidism with levothyroxine – see section 7 for more information. If patients become thyrotoxic refer for specialist endocrine advice immediately.<br>• **Eye disorders** - corneal micro deposits occur almost always in patients on continuous therapy. They may be associated with dazzling light or blurred vision. Corneal micro-deposits consist of complex lipid deposits and are reversible following discontinuation of treatment and do not require discontinuation of amiodarone. Optic neuropathy and/or optic neuritis require amiodarone withdrawal. Drivers should be advised that this may cause them to be dazzled by headlights at night.<br>• **Hepato-biliary disorders** - increases in serum transaminases are very common early in therapy and these may resolve spontaneously, or with reduction of dosage. Acute liver disorders, with high transaminases/jaundice have been reported. Very rarely chronic liver reactions have been seen, including hepatitis and cirrhosis. See monitoring requirements below.<br>• **Respiratory** - pulmonary toxicity is a common side effect and patients should be advised to report new respiratory problems.<br>• **Skin** - photosensitivity is very common and patients should be cautioned to avoid exposure of skin to direct sunlight or sun lamps. A wide spectrum sunscreen should be used to protect against both long ultraviolet and visible light. Amiodarone may also cause slate-grey pigmentation of the skin. This is slowly reversible on discontinuation of treatment.<br><br>**The patient should be advised to report any of the following signs or symptoms without delay:**<br>• Increasing breathlessness, dyspnoea or non-productive cough<br>• Altered vision<br>• Loss of appetite/weight loss<br>• Sleep disturbance/nightmares<br>• Tremor/loss of coordination<br><br>**If you suspect an adverse reaction has occurred please contact the patient's cardiologist.** |

**Drug interactions**

Amiodarone has an average half life of 50 days although there can be considerable interpatient variation from 20 days up to 100 days. Therefore there is potential for interactions to occur for several weeks after treatment with amiodarone has been stopped.

This is a list of commonly occurring drug interactions:

- **Anticoagulants** - amiodarone enhances the anticoagulant effect of warfarin, phenindione and dabigatran. The interaction between amiodarone and warfarin is well documented and clinically important and it appears to occur in most patients. The potentiation of warfarin starts within a few days of starting concurrent amiodarone and is usually maximal by 2 to 7 weeks. Ideally the dose of warfarin should be reduced when amiodarone is commenced based on INR measurements. The dose of warfarin should initially be reduced by approximately 25%-50% when amiodarone is added to established anticoagulant treatment, with increased INR monitoring on a weekly basis until a new steady-state is achieved. If established amiodarone therapy is withdrawn in a patient taking warfarin, it is likely that the dose of warfarin will need increasing gradually over the first few months after amiodarone is stopped. This is because amiodarone has such a long half-life. If warfarin is required in a patient on established amiodarone therapy, a lower initial dose of warfarin should be used. In patients stabilised on warfarin and amiodarone, the possibility of amiodarone-induced thyroid dysfunction should be considered if an abrupt increase in INR occurs.
- **Digoxin** - increases plasma concentration of digoxin and digoxin dose usually requires to be halved.
- **Flecainide** - plasma concentration of flecainide is increased and dose of flecainide usually requires to be halved.
- **Diltiazem, verapamil and beta blockers** - increased risk of bradycardia, AV block and myocardial depression.
- **Phenytoin** - serum phenytoin levels can be raised by amiodarone, markedly so in some individuals and phenytoin toxicity may occur. Monitor phenytoin levels and for adverse effects (e.g. blurred vision, nystagmus, ataxia or drowsiness) and reduce the phenytoin dose as necessary. Amiodarone serum levels can be reduced by phenytoin.
- **Any medication that prolongs QTc interval** - this may increase the risk of torsades de pointes if used in combination with amiodarone. These include Class 1a and Class III antiarrhythmic drugs e.g. quinidine, procainamide, disopyramide and sotalol; IV erythromycin, co-trimoxazole or pentamidine injection; antipsychotics; quinolone antibiotics; lithium and tricyclic antidepressants; antimalarials; and the antihistamine mizolastine. Concomitant use of these medicines is contra-indicated with amiodarone. If further advice is required, this should be discussed with the cardiologist. Citalopram and domperidone may also prolong

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| | the QT interval. For a list of medicines that prolong the QT interval see http://www.sads.org/living-with-sads/drugs-to-avoid<br>• **Grapefruit juice** - inhibits cytochrome P450 3A4 and may increase the plasma concentration of amiodarone. Patients should be advised to avoid drinking grapefruit juice.<br>• **Stimulant laxatives** - may cause hypokalaemia thus increasing the risk of torsades de pointes; other types of laxatives should be used.<br>• Caution should be exercised over combined therapy with the following drugs which may cause hypokalaemia and/or hypomagnesaemia: diuretics, systemic corticosteroids, tetracosactide, and intravenous amphotericin.<br>• **Hepatitis C medicines**<br><br>Risk of severe bradycardia or heart block when amiodarone is used in combination with some medicines used to treat hepatitis C e.g. daclatasvir, simeprevir, sofosbuvir and telaprevir (brand names of combination hepatitis C medicines include Harvoni®, Viekirax® and Exviera®). Please use the following link to check for interactions :<br>University of Liverpool Hep-drug interactions and discuss with hepatitis C team.<br><br>If concomitant use with amiodarone cannot be avoided because other anti-arrhythmics are not tolerated or contraindicated, patients should be closely monitored, particularly during the first weeks of treatment. Patients at high risk of bradycardia should be monitored continuously for 48 hours in an appropriate clinical setting after starting concomitant treatment. Also monitor patients who have stopped amiodarone within the last few months and need to start hepatitis C medications. 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.<br><br>**Drugs metabolised by cytochrome P450 3A4:**<br>When drugs are co-administered with amiodarone, an inhibitor of CYP 3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity:<br>• **Ciclosporin** - plasma levels of ciclosporin may increase as |

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| | much as 2-fold when used in combination. A reduction in the dose of ciclosporin may be necessary to maintain the plasma concentration within the therapeutic range.<br>• **Statins** - the risk of muscular toxicity is increased by concomitant administration of amiodarone with statins metabolised by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolised by CYP 3A4 when given with amiodarone. The manufacturer of simvastatin recommends using a maximum of 20mg and atorvastatin a lower maximum dose.<br>• Other drugs metabolised by cytochrome P450 3A4: examples of such drugs are lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine and ergotamine.<br><br>**Cautions:**<br>• Hypokalaemia (measure serum-potassium concentration before treatment), heart failure, elderly<br><br>**Contraindications:**<br>Amiodarone is contraindicated in:<br>• Patients with sinus bradycardia and sino-atrial heart block. (Note: it should be used only in conjunction with a pacemaker in patients with severe conduction disturbance or sinus node disease).<br>• Patients with evidence or history of thyroid dysfunction or known hypersensitivity to iodine or amiodarone.<br>• Combination with drugs that increase the risk of torsades de pointes.<br>• Pregnancy (unless exceptional circumstances).<br>• Breast feeding. |
| **7. Monitoring** | **Baseline investigations**<br>**To be undertaken by Cardiology Clinic, Secondary Care**<br>• Pulmonary function tests – spirometry and DCLO<br>• Chest X-ray (ensure chest X-ray within last 12 months)<br>• Thyroid function tests ($T_3$, $T_4$, and TSH)<br>• Liver function tests<br>• Urea and electrolytes, (in particular check for hypokalaemia) creatinine,<br>• ECG<br><br>Consideration could be given to examination of the skin, eyes and neurological systems at base-line and review at clinic.<br><br>**To be undertaken by Primary Care**<br>**Liver function tests:** Every 6 months<br><br>*Initial elevation of serum transaminases can occur and these may resolve spontaneously, or with reduction of dosage. Rarely, acute liver disorders may occur that warrants withdrawal of treatment. It* |

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| | *is difficult to be certain of appropriate action if LFTs change. The cardiologist should be contacted if there are any concerns about raised LFTs.*<br><br>**Thyroid Function Tests:** (including free thyroid hormone levels)<br>At initiation of therapy, then (if normal) every 6 months. Thyroid function tests should be monitored again 12 months after discontinuation of therapy.<br><br>Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism may occur. Clinical assessment alone is unreliable, and laboratory tests should be performed before treatment and every 6 months. Thyroxine (T4) may be raised in the absence of hyperthyroidism; therefore tri-iodothyronine (T3), T4, and thyroid-stimulating hormone (thyrotrophin, TSH) should all be measured. A raised T3 and T4 with a very low or undetectable TSH concentration suggests the development of thyrotoxicosis. The thyrotoxicosis may be very refractory, and amiodarone should usually be withdrawn at least temporarily to help achieve control; treatment with carbimazole may be required. If the patient becomes thyrotoxic refer for specialist endocrine advice immediately. If treatment withdrawal is recommended this should first be discussed with the patient's cardiologist.<br><br>Hypothyroidism can be treated with replacement therapy without withdrawing amiodarone if it is essential; careful supervision is required.<br><br>**Cardiac:**<br>ECG to be done at baseline in Cardiology clinic, secondary care only, unless the patient is started on any medicines which may lengthen the QT interval. Please see list at: http://www.sads.org/living-with-sads/drugs-to-avoid<br><br>At all other follow-up appointments ECG monitoring is not required and monitor patient based on pulse and symptoms.<br><br>**Chest X-ray:**<br>Should be repeated by secondary care if the patient develops symptoms of respiratory disease. Discuss with cardiologist.<br><br>*The usual finding is of upper lobe fibrosis. If no cause for the respiratory symptoms is evident clinically or radiologically the patient should be referred promptly for specialist investigation by a respiratory physician.*<br><br>**Pulmonary function tests:**<br>During treatment if pulmonary toxicity is suspected, a chest X ray should be repeated and lung function testing should be undertaken by secondary care. Lung function testing should include, where possible, measurement of transfer factor. Initial radiological changes may be difficult to distinguish from pulmonary venous congestion. Pulmonary toxicity has usually been reversible following early withdrawal of amiodarone therapy, with or without corticosteroid therapy. Clinical symptoms often |

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| | resolve within a few weeks followed by slower radiological and lung function improvement. Some patients can deteriorate despite discontinuing amiodarone tablets.<br><br>**Ophthalmological Examination:**<br>Routine ophthalmological examination is not required.<br>Micro deposits may be evident but these rarely cause any symptoms. Patients should be advised to inform their optometrist that they are taking amiodarone and to attend for annual eye examinations. Any changes in vision should be investigated. |
| **8. Pharmaceutical aspects** | Do not store above 25 $^{0}$C. |
| **9. Secondary care contact information** | Dr Stephan Koch<br>Consultant Cardiologist<br>Ninewells Hospital<br>01382 660111 bleep 4396<br>skoch@nhs.net<br><br>Connie Dunbar<br>BHF Arrhythmia Nurse Specialist<br>Ninewells Hospital<br>01382 632193 (ext 32193)<br>Mob: 07964 243577<br>connie.dunbar@nhs.net<br><br>Susan Bowles<br>Specialist Pharmacist Cardiovascular and Medicine<br>Ninewells Hospital<br>01382 660111 (bleep 4276)<br>susanbowles@nhs.net |
| **10. Responsibilities of initiating consultant** | • To assess the suitability of the patient for treatment.<br>• Ensure that the patient/carer has received counseling and understands the therapy, its benefits, limitations, monitoring requirements, adverse effects and is aware of actions to take if adverse effects are suspected.<br>• Inform the GP of the information given to the patient<br>• To review patient at agreed intervals<br>• Carry out disease and initial drug monitoring as described in section 7.<br>• If patient is on warfarin advise patient of need for weekly INR monitoring once amiodarone started. |
| **11. Responsibilities of primary care** | **General and Prescribing:**<br>• To reply to the request for shared care within 2 weeks of receipt of the consultant letter.<br>• Prescribe follow up prescriptions for amiodarone- ensure continued prescribing of amiodarone remains clinically appropriate at dose advised by initiating team<br>• Notify consultant if treatment with amiodarone is discontinued. |

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| | • Ensure there are no drug interactions with any other medications initiated in primary care<br><br>**Disease & drug monitoring:**<br>• Carry out monitoring as described in section 7 and communicate abnormal results to the consultant cardiologist.<br>• Urgent drug discontinuation/ referral to specialist as clinically appropriate<br>• To stop treatment on the advice of the specialist.<br>• To refer back to the specialist if the patient's condition deteriorates.<br>• Identify adverse effects to amiodarone and report these to the specialist and where appropriate to the Commission on Human Medicines/MHRA (Yellow card scheme). |
| **12. Responsibilities of patients** | • Report any possible adverse reactions to the GP – e.g. new respiratory problems.<br>• Avoid exposure of skin to direct sunlight or sun lamps during treatment and for several months after stopping<br>• Avoid grapefruit juice<br>• If taking a statin and amiodarone, report any signs of unexplained muscle pain, tenderness or weakness or dark coloured urine.<br>• Ensure they have an adequate supply of medication.<br>• Attend appointments |
| **13. Supporting documentation** | *See attached patient information leaflet* |

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| **14. Patient monitoring booklet** | *See attached patient information leaflet* |
| **15. GP letter** | *Attached below* |
| **16. Consultation** | Developed by Susan Bowles, Pharmacist, Dr Stephan Koch, Consultant Cardiologist and Connie Dunbar, Arrhythmia Nurse Specialist all Ninewells Hospital Dundee<br><br>Commented on by Consultant Cardiologists Ninewells Hospital and Perth Royal Infirmary<br><br>Commented on by Kathryn Bendall and Kenny Halliday Locality Pharmacists NHS Tayside<br><br>Commented on by GP representatives<br><br>Commented on by a patient representative |
| **17. Relevant** | BNF October 2014 accessed at |

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| **references** | https://www.medicinescomplete.com/mc/bnf/current/index.htm on 17/10/14<br><br>Amiodarone 200mg tablets Summary of Product Characteristics accessed on electronic medicines compendium at http://www.medicines.org.uk Last updated 07/05/2014. Accessed on 17/10/14<br><br>Stockley's Drug Interactions accessed at https://www.medicinescomplete.com/mc/stockley/current/ on 17/10/14<br><br>Scottish Drug Tariff accessed at http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/ on 17/10/14<br><br>Camm AJ, Arden C, Choy A, Kaba R, Keane D, Khan K *et al* Translating regulatory advice into practice: use of dronedarone and older anti-arrhythmics in AF management *The British Journal of Cardiology* 2012;19:e2-e8<br><br>Based on an original document prepared by pharmacists at York Teaching Hospital NHS Foundation Trust |
| **Agreement date** | January 2015 |
| **Agreement review date** | January 2017 |

Consultant Request

***IMPORTANT: ACTION NEEDED**

Dear Dr

Patient name:

CHI:

Diagnosis:

This patient is suitable for treatment with amiodarone for the treatment of *(insert indication)*

This drug has been accepted for Shared Care by ADTC and Primary Care services.

The Shared Care Agreement can be viewed on staffnet under pharmacy: medicines governance.

I am therefore requesting your agreement to share the care of this patient.

Treatment was* / should be* started on (*insert date started*) (*insert dose*)

If you are in agreement, please undertake monitoring and treatment from *(insert date*)

The following baseline monitoring/tests have been undertaken by secondary care:

- Pulmonary function tests / Chest X-ray
- Thyroid function tests / Liver function tests
- Urea and electrolytes, creatinine / ECG

Tests to be undertaken by primary care:

- 6 monthly liver function test monitoring
- 6 monthly thyroid function test monitoring and thyroid function test repeated 12 months after discontinuation of amiodarone.

Next review with this department: *(add date)*

You will be sent a written summary within 14 days.

Please use the reply slip overleaf and return it as soon as possible.
Thank you.

Yours

*Signature*

Consultant name

* *delete as applicable*

Adapted from the WMP document for development of shared care agreements, developed on behalf of AWPAG

**GP Response to Shared Care Request**

Dear Dr

Patient: *(Insert Patients name)*

Identifier: *(Insert Patient CHI/address)*

I have received your request for shared care of this patient who has been advised to start amiodarone.

A I am willing to undertake shared care for this patient as set out in the protocol

B I wish to discuss this request with you

C I am unable to undertake shared care of this patient because (*please state reason/s)*

GP Signature: Date:

GP Address/Practice stamp:

* *delete as applicable*