Therapeutics Advisory Group

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Norfolk and Waveney Integrated Care System

NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT FRAMEWORK

Shared care guidelines for Use of Dronedarone in Adult Services
Monitoring level 2 - Prescribe the drug and perform a more intense level of monitoring, e.g. quarterly

Generic and Proprietary/Brand Name	
Dronedarone / Multaq®	
Indications for shared care	
Licensed indication: maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation	
Specialist Prescribing and Monitoring Responsibilities	**GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities**
• Assess the patient, provide diagnosis and communicate to primary care. • Discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling to enable the patient to reach an informed decision. • Provide an appropriate patient information leaflet. • Assess for contraindications, cautions and interactions • Conduct required baseline investigations and initial monitoring • Initiate and optimise treatment. Prescribe the maintenance treatment for at least 4 weeks and until optimised. • Once treatment is optimised, complete the shared care documentation and send to 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 • Prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care. • Conduct the required reviews and monitoring 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 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.	• Accept shared care agreement and prescribe ongoing treatment as detailed in the request, taking into any account potential drug • Adjust the dose of dronedarone prescribed as advised by the specialist. • Conduct the required monitoring • Communicate any abnormal results to the specialist. • Manage adverse effects as detailed and discuss with specialist team when required. • Stop dronedarone and make an urgent referral to the specialist if if ECG changes, hepatotoxicity, pulmonary toxicity or renal toxicity are suspected. • Refer the management back to the specialist if the patient becomes or plans to become pregnant. • Stop treatment as advised by the specialist.

Patient Information

- Take dronedarone as prescribed and avoid abrupt withdrawal unless advised by the primary care prescriber or specialist.
- Attend regularly for monitoring and review appointments with primary care and specialist, and keep contact details up to date with both prescribers. Be aware that medicines may be stopped if they do not attend.
- Report adverse effects to their primary care prescriber. Seek immediate medical attention if they develop any symptoms as detailed in section 11.
- Report the use of any over the counter medications to their prescriber and be aware they should discuss the use of dronedarone with their pharmacist before purchasing any OTC medicines.
- Avoid grapefruit juice while taking dronedarone.
- Patients of childbearing potential should take a pregnancy test if they think they could be pregnant, and inform the specialist or GP immediately if they become pregnant or wish to become pregnant.

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:

- Signs or symptoms of pulmonary toxicity, e.g. breathlessness, non-productive cough or deterioration in general health (e.g. fatigue, weight loss, fever)
- Signs or symptoms of liver injury, e.g. abdominal pain, loss of appetite, nausea, vomiting, fever, malaise, fatigue, itching, dark urine, or yellowing of skin or eyes
- Signs or symptoms of heart failure, e.g. development or worsening of weight gain, dependent oedema, or dyspnoea
- Signs or symptoms of bradycardia, e.g. dizziness, fatigue, fainting, shortness of breath, chest pain or palpitations, confusion or trouble concentrating

The patient should be advised:

- Avoid grapefruit and grapefruit juice while taking dronedarone.
- If taking a statin and dronedarone, to report any signs of unexplained muscle pain, tenderness, weakness or dark coloured urine.
- Photosensitivity is an uncommon side effect of dronedarone (less than 1 in 100 people). If it occurs, patients should be advised on appropriate self-care: e.g. sun avoidance, protective clothing, avoiding tanning (including tanning beds) and to purchase and use of a wide broad spectrum sunscreen (at least SPF30). These measures should be continued for the duration of therapy.

Specialist Contact Details

Norfolk and Norwich University Hospital NHS Foundation Trust

First line contact should be made with the initiating consultant. Where this is not possible, the duty cardiology specialist registrar should be contacted and they will discuss with the most appropriate available consultant colleague.

Contact should be made through the NNUHFT switchboard: 01603 2868286 or Dr Metcalf's secretary (Medicine for the Elderly): 01603 289439

Further drug information on dronedarone can be obtained from:
NNUH Pharmacy Department Medicines Information: 01603 287139
Other Acute Hospital Contacts:
The Queen Elizabeth Hospital, King's Lynn switchboard: 01553 613613
The James Paget University Hospital switchboard: 01493 452452

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.
- **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment

Dronedarone is used in the treatment of severe cardiac rhythm disorders, as a second line option when other drugs are ineffective or contraindicated. It has potentially serious adverse effects and its use requires monitoring both clinically and via laboratory testing.

Due to the significant safety concerns, NHS England (NHSE) and NHS Improvement's guidance advises that prescribers should not initiate dronedarone in primary care for any new patients. In exceptional circumstances, if there is a clinical need for dronedarone to be prescribed, this must be initiated by a specialist and only continued under a shared care arrangement in line with NICE clinical guidance (Atrial fibrillation: NG 196). Dronedarone should be used as recommended in NICE TA 197 Dronedarone for the treatment of non-permanent atrial fibrillation
Where there is an existing cohort taking dronedarone, it is recommended that these patients be reviewed to ensure that prescribing remains safe and appropriate.

This document applies to adults aged 18 and over.

Licenced use and agreed local off-label use

Licensed indication: maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation

- 2nd line use after beta blockers where amiodarone is contraindicated, or
- 3rd line use if amiodarone has been tried but not tolerated*
- Not for use in the setting of permanent AF

* NB Dronedarone is contra-indicated in patients with liver or lung toxicity related to previous use of amiodarone

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NICE TA 197 recommends dronedarone as an option in patients:

- whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option and after alternative options have been considered **and**
- who have at least 1 of the following cardiovascular risk factors:
- hypertension requiring drugs of at least 2 different classes
- diabetes mellitus
- previous transient ischaemic attack, stroke or systemic embolism
- left atrial diameter of 50 mm or greater **or**
- age 70 years or older and
- who do not have left ventricular systolic dysfunction **and**
- who do not have a history of, or current, heart failure

As per RMOC, there are no appropriate off-label indications

Criteria for Patient Selection

Amiodarone is an option in the treatment of paroxysmal or recurrent persistent AF where other agents (including beta-blockers, calcium channel blockers, Class 1c agents (e.g. flecainide, propafenone) and sotalol) are ineffective, contraindicated or not tolerated.

Dronedarone can be considered as an alternative to amiodarone in the following circumstances:

1) Demonstrated contraindication to amiodarone:
a. Amiodarone-induced or pre-existing history of thyrotoxicosis

2) Intolerance of amiodarone
a. Specific allergic response
b. Intolerable GI disturbance
c. Unacceptable photo-sensitisation or additional risk (skin malignancy - excluding patients with solar keratosis, who are usually managed with total sunblock and advice on avoiding sun exposure.)

3) Specific issues or concerns surrounding anti-coagulation. E.g. where the enhancement of the anticoagulant effect of warfarin by amiodarone may lead to unacceptable clinical risk in individual cases (e.g. in patients with intracerebral bleed in the last year, GI haemorrhage in the last 3 months).

The Multaq® SPC also states that "*Clinically significant INR elevations (≥5) usually within 1 week after starting dronedarone have been reported in patients taking oral anticoagulants. Consequently, INR should be closely monitored after initiating dronedarone in patients taking vitamin K antagonists as per their label*." (http://www.medicines.org.uk/emc/)

Specific pro-arrhythmic risk (unacceptable QT prolongation on amiodarone)

Form and strength of preparation

400 mg film-coated tablets

Side Effects and Management

Link to BNF

Link to SPC

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

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

Result	**Action for primary care**
Renal function: Electrolyte deficiency: hypokalaemia / hypomagnesaemia	Continue dronedarone. Correct deficiency as per local guidelines.
Creatinine elevated from baseline	**Stop dronedarone** for any elevations of serum creatinine which occur after transfer to primary care. Discuss urgently with specialist
Creatinine clearance <30 mL/minute/ 1.73m^2	**Stop dronedarone** and refer urgently to the specialist.

Cardiovascular: Bradycardia: Heart rate 50 - 60bpm without symptoms	Continue dronedarone. Repeat monitoring. No action required if hear rate remains >50 without symptoms.
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 dronedarone.** Urgent referral to specialist team.
Recurrence of atrial fibrillation	Refer to specialist team; discontinuation should be considered. Discontinue dronedarone if patient develops permanent AF with a duration of six months or more.
Signs or symptoms of congestive heart failure, e.g. weight gain, dependent oedema, or increased dyspnoea.	**Stop dronedarone** if congestive heart failure is suspected and refer urgently to specialist team.
Hepatotoxicity: Serum transaminases >5xULN or any symptoms of hepatic injury	**Stop dronedarone**. Urgent referral to initiating specialist and hepatologist.
ALT elevated >3xULN but no symptoms of hepatic injury	Continue dronedarone and repeat LFTs in 48-72 hours. If still elevated **stop dronedarone** and discuss with specialist urgently.
Symptoms of hepatic injury (e.g. hepatomegaly, weakness, ascites, jaundice)	Check LFTs urgently; proceed as above.
Pulmonary toxicity: new/worsening cough, shortness of breath or deterioration in general health (e.g. fatigue, weight loss, fever)	Continue dronedarone**.** Urgent referral to initiating specialist and respiratory specialist.
Gastrointestinal disturbance: diarrhoea, nausea, vomiting, abdominal pain, dyspepsia	Continue dronedarone. May require dose reduction; discuss with specialist if persistent.
General disorders: fatigue, asthenia	Continue dronedarone. May require dose reduction; discuss with specialist.
Dermatological disorders: rashes, pruritus, photosensitivity	Continue dronedarone. Reinforce appropriate self-care, including sun avoidance and purchasing of a broad spectrum sunscreen (at least SPF30) if photosensitivity occurs. May require dose reduction; discuss with specialist.

Drug Interactions

Link to BNF

Link to SPC

Cautions and Contraindications

Link to BNF

Link to SPC

Initiation of therapy

- Transfer of monitoring and prescribing to primary care is normally after the patient's dose has been optimised and with satisfactory investigation results for at least 4 weeks
- 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 and maintenance dose:

400mg twice daily, with the morning and evening meals.

The starting and initial maintenance dose must be prescribed by the initiating specialist. Treatment should be initiated and monitored only under specialist supervision.

Administration Information

Tablets should be swallowed whole with a drink of water during a meal. The tablet cannot be divided into equal doses and should not be split.

If a dose is missed, patients should take the next dose at the regular scheduled time and should not double the dose.

Grapefruit juice should be avoided during treatment with dronedarone

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.

Baseline, initial monitoring and ongoing assessment – by Specialist

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:

- Liver function tests (LFTs)
- Urea and electrolytes (U&Es), including potassium, magnesium, and serum creatinine
- Electrocardiogram (ECG)

Initial monitoring:

- Liver function tests: after 7 days of treatment, after 1 month of treatment, then monthly until prescribing is transferred to primary care
- Urea and electrolytes: after 7 days of treatment, and after a further 7 days if any elevation is observed. If serum creatinine continues to rise then consideration should be given to further investigation and discontinuing treatment.
- Monitor concurrent medicines as appropriate, e.g. anticoagulants, digoxin.

Ongoing monitoring:

- ECG, at least every six months

- 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 remains appropriate.

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

GP / Community Team or other Primary Care monitoring responsibilities

Monitoring	Frequency
Urea and electrolytes (including magnesium and potassium) and creatinine clearance.	Every 6 months
Liver function tests	Monthly for the first 6 months of treatment, and at month 9 and month 12 Every 6 months thereafter
Symptoms of heart failure, e.g. development or worsening of weight gain, dependent oedema, or dyspnoea	Ongoing
ECG (monitoring may be conducted in primary care where this service is available)	At least every six months

Consultant / Specialist prescribing responsibilities

- Assess the patient, provide diagnosis and communicate to primary care.
- Discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling to enable the patient to reach an informed decision.
- Provide an appropriate patient information leaflet.
- Assess for contraindications, cautions and interactions
- Conduct required baseline investigations and initial monitoring
- Initiate and optimise treatment. Prescribe the maintenance treatment for at least 4 weeks and until optimised.
- Once treatment is optimised, complete the shared care documentation and send to 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
- Prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care.
- Conduct the required reviews and monitoring 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 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.

GP prescribing responsibilities

- Accept shared care agreement and prescribe ongoing treatment as detailed in the request, taking into any account potential drug
- Adjust the dose of dronedarone prescribed as advised by the specialist.
- Conduct the required monitoring
- Communicate any abnormal results to the specialist.
- Manage adverse effects as detailed and discuss with specialist team when required.
- Stop dronedarone and make an urgent referral to the specialist if if ECG changes, hepatotoxicity, pulmonary toxicity or renal toxicity are suspected.
- Refer the management back to the specialist if the patient becomes or plans to become pregnant.
- Stop treatment as advised by the specialist.

Pregnancy, Paternal Exposure and Breastfeeding

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:
There are limited data on the use of dronedarone in pregnant women. Studies in animals have shown reproductive toxicity. Use is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding:
Low levels of dronedarone are anticipated in breast milk. Use is cautioned while breast feeding; infants should be monitored for adverse events such as diarrhoea, vomiting, weakness, bradycardia.

Indications for referral back to Specialist

- Stop dronedarone and make an urgent referral to the specialist if if ECG changes, hepatotoxicity, pulmonary toxicity or renal toxicity are suspected.
- Refer the management back to the specialist if the patient becomes or plans to become pregnant.
- Stop treatment as advised by the specialist.

Further information and supporting documents

- eBNF accessed via www.medicinescomplete.com on 12/04/2021
- Dronedarone hydrochloride 400 mg film-coated tablets (Multaq®). Sanofi. Date of revision of the text: 02/06/2020. Accessed via https://www.medicines.org.uk/emc/product/497/ on 09/04/2021.
- Dronedarone hydrochloride 400 mg film-coated tablets (Dronedarone Aristo). Aristo Pharma. Date of revision of the text: 14/10/2020. Accessed via https://www.medicines.org.uk/emc/ on 09/04/2021
- NHS England and NHS Clinical Commissioners. Aug 2019. https://www.england.nhs.uk/publication/items-which-should-not-be-routinely-prescribed-in-primary-care-guidance-for-ccgs/ Accessed 09/04/2020
- MHRA. Drug Safety Update volume 5 issue 3: A1. October 2011. Dronedarone (Multaq▼): cardiovascular, hepatic and pulmonary adverse events – new restrictions and monitoring requirements. Accessed via https://www.gov.uk/drug-safety-update/dronedarone-multaq-cardiovascular-hepatic-and-pulmonary-adverse-events-new-restrictions-and-monitoring-requirements on 09/04/2021
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Author(s) and Organisation	Adapted for local use by Jen Carroll, TAG Lead Technician, from RMOC Shared Care Protocol – 'Dronedarone for patients within adult services' and existing local agreement by Dr Ian Williams,

	Consultant Cardiologist and Catherine Heywood, Pharmacy Teacher Practitioner, NNUH / Fiona Marshall TAG Lead Pharmacist
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1.	December 2011	Dr Ian Williams, Consultant Cardiologist and Catherine Heywood, Pharmacy Teacher Practitioner, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Discussed and approved in principle by the Therapeutics Advisory Group (TAG) November 2011. Final version approved by the TAG Support Group, December 2011.
2.1	December 2013	Dr Ian Williams, Consultant Cardiologist and Catherine Heywood, Pharmacy Teacher Practitioner, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	For consideration by the TAG January 2014
2.2	January 2014	Dr Ian Williams, Consultant Cardiologist and Catherine Heywood, Pharmacy Teacher Practitioner, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	TAG and NNUH DT&MMC recommended that monitoring / prescribing responsibility should remain with the specialist until one month after initiation of treatment. Related changes made to the document and highlighted for the attention of the authors. Document returned to the authors for their consideration on 28th January 2014. Accepted by the authors 14th February 2014.
3.0	March 2017	As for 2.2. Also sent to Dr Julian Boullin, Consultant Cardiologist, NNUH	Draft under review	Updated with current TAG template format. Checked against current SPC - Co-administration with dabigatran added to

				contraindications and precautions. Sent to authors for review and comment for possible consideration by the TAG – May 2017.
3.1	April 2017	As for 2.2.	Draft for reconsideration by the TAG – May 2017.	Advice from authors to add further information on NOACs to the drug interactions section.
3.2	May 2017	As for 2.2	Current	Supported by the TAG – May 2017
4.0	Aug 2021	Jen Carroll, TAG Lead Technician	FINAL	Discussed at August 2021 TAG meeting. Review dates extended for a year from meeting due to covid pressures
5.0	Nov 2022	Jen Carroll, TAG Lead Technician	Draft	Adapted for local use from RMOC Shared Care Protocol – ' Dronedarone for patients within adult services' and from existing local shared care agreement
5,1	Feb 2023	Jen Carroll, TAG Lead Technician	Final	Ratified by Planned Care and Medicines Management Working Group