Shared Care Protocol
Dronedarone for non-permanent atrial fibrillation

This shared care protocol (SCP) sets out details for the sharing of care for ***patients prescribed dronedarone in the management of non-permanent atrial fibrillation.***

It should be read in conjunction with the latest Summary of Products Characteristics (SmPC) available at http://www.medicines.org.uk/emc/

As outlined in NHS England Guidance 2018 (07573), 'Responsibility for Prescribing Between Primary & Secondary/Tertiary Care': When a specialist considers a patient's condition to be stable or predictable, they may seek the agreement of the GP concerned (and the patient) to share their care.

This document provides information on drug treatment for the shared commitment between the specialist and GP concerned. GPs are invited to participate. If the GP is not confident to undertake these roles, then 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. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

N.B. If the GP decides not to participate in shared care for a particular patient, they must inform the relevant specialist in writing, within 2 weeks of receipt of a request to share care.

Introduction

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

This document applies to adults aged 18 and over.

MHRA/CHMP advice:
Dronedarone (Multaq▼): cardiovascular, hepatic and pulmonary adverse events – new restrictions and monitoring requirements - GOV.UK (www.gov.uk)

European Medicines Agency recommends restricting use of Multaq | European Medicines Agency (europa.eu)

For further information please click on the links below or visit:

- https://bnf.nice.org.uk/
- NICE TA197 Dronedarone for the treatment of non-permanent atrial fibrillation
- NICE NG196 Atrial fibrillation: diagnosis and management
- Summary of Product Characteristics - Dronedarone
- Dronedarone Aristo Prescriber_Guide_ver04 (medicines.org.uk)
- MULTAQ® (Dronedarone) Prescriber Guide v2.0 Oct 2021

Licensed indication:

Dronedarone is indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF).

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

Dose (posology & method of administration):

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

For full details see SmPC

Contra-indications: For full details see SmPC

- Known hypersensitivity to dronedarone or any of the excipients
- Second- or third-degree atrio-ventricular block, complete bundle branch block, distal block, sinus node dysfunction, atrial conduction defects, or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Bradycardia less than 50 beats per minute
- Permanent atrial fibrillation (AF) with an AF duration ≥6 months (or duration unknown), and attempts to restore sinus rhythm no longer considered by the physician
- Unstable haemodynamic conditions
- History of or current heart failure, or left ventricular systolic dysfunction
- Patients with liver or lung toxicity related to previous use of amiodarone

- Co-administration with potent cytochrome P450 3A4 (CYP3A4) inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir
- Co-administration with medicinal products inducing torsades de pointes, including phenothiazines, cisapride, bepridil, tricyclic antidepressants, terfenadine and certain oral macrolides (such as erythromycin), class I and III anti-arrhythmics
- Co-administration with dabigatran
- QTc Bazett interval greater than 500 milliseconds
- Severe hepatic or renal impairment (CrCl <30 mL/min)

Cautions:

Dronedarone can cause serious adverse reactions; clinical monitoring for development of congestive heart failure, left ventricular systolic dysfunction, QTc prolongation, liver injury, and respiratory disease are required.

For full details see SmPC

Special warnings and precautions: For full details see SmPC

Drug interactions:

Dronedarone is associated with a large number of interactions, some of which are significant enough to contradict concurrent use, require dose adjustment and/or additional monitoring.

Dronedarone is contraindicated when co-administered with potent cytochrome P450 3A4 (CYP3A4) inhibitors, medicinal products inducing torsades de pointes, and dabigatran.

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

- P-glycoprotein (PgP) substrates (e.g. digoxin, dabigatran, apixaban, rivaroxaban, edoxaban).
- CYP3A4 substrates (e.g. ciclosporin, statins, fentanyl, sildenafil, tacrolimus, sirolimus, everolimus, apixaban, rivaroxaban, edoxaban).
- CYP2D6 substrates (e.g. metoprolol).

Dronedarone interacts with other medicines that:

- Induce Torsade de Points or prolong QTc (e.g. Phenothiazines, cisapride, bepridil, tricyclic antidepressants, certain oral macrolides (such as clarithromycin and erythromycin), terfenadine and Class I and III anti-arrhythmics). Concomitant use is contraindicated.
- Lower heart rate (e.g. Beta-blockers, calcium channel blockers).
- Induce hypokalaemia (e.g. Diuretics, stimulant laxatives).
- Induce hypomagnesaemia (e.g. Diuretics).

Other interactions include:

- CYP3A4 inhibitors – may increase exposure to dronedarone (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir, clarithromycin, grapefruit juice). Concomitant use is contraindicated.
- Potent CYP3A4 inducers – may reduce exposure to dronedarone and are not recommended (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin, St John's Wort).
- Anticoagulants – vitamin K antagonist and direct oral anticoagulant (DOAC) exposure may be increased by dronedarone (e.g. warfarin, rivaroxaban, edoxaban).

The above list is not exhaustive. See BNF or SmPC for comprehensive information and recommended management.

Fertility, pregnancy & lactation:

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

Adverse effects & management:

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

See ***Table 1: 'Adverse effects and other management'*** for the management of adverse effects and test results by primary care.

For full information and incidence of adverse effects see relevant SmPC

Advice to patients & carers:

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

Shared Care Responsibilities

Consultant responsibilities:

1. Ensure patient fulfils MHRA/CHMP criteria for dronedarone therapy before initiation.
2. Ensure **baseline investigations** are performed before dronedarone is initiated.
   - Liver function tests (**LFTs**)
   - Urea and electrolytes (**U&Es**), including potassium, magnesium, and serum creatinine
   - Electrocardiogram (**ECG**)
3. Ensure treatment with Class I or III antiarrhythmics (such as flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol, amiodarone) is stopped before dronedarone is initiated.
4. Counsel the patient/carer regarding the benefits and risks of treatment and provide the patient/carer with any relevant information and advice, including the patient information leaflet (PIL) for dronedarone. See also '*Advice to patients & carers'.*
5. Initiate treatment with dronedarone, ensuring patient/carer has a basic understanding of what the drug is, how and when it should be taken, why it is being used, and an awareness of potential side effects.
6. Ensure patient/carer understands, and can comply with, the monitoring requirements.
7. Provide advice on the need for contraception to patients of childbearing age on initiation and at each review.
8. Notify the patient's GP that dronedarone has been initiated and report progress following each clinic review.
9. Prescribe at least one month's worth of dronedarone treatment.
10. **Initial monitoring:**
    - **LFT's**: after 7 days of treatment, after 1 month of treatment, then monthly until prescribing is transferred to primary care
    - **U&E's**: 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.
11. **Provide patient with completed blood form (for day 7 serum creatinine and liver function tests) and book appointment with GP**
12. Once the consultant considers the patient's condition is stable on a dose effective for arrhythmia control, a request can be made to the patient's GP to 'share' the patient's care.
13. The patient/carer should be informed of arrangements for further prescriptions.
14. All patients will remain under the ongoing care of a named consultant.
15. The consultant will provide support if problems occur using the contact details provided.
16. The consultant will give directions as to when treatment should be discontinued.

General Practitioner responsibilities:

1. Accept request to take on prescribing of dronedarone once the consultant considers a patient's condition is stable and the patient is stabilised on a tolerated dose effective for arrhythmia control, no sooner than one month after initiation.
2. Reinforce educational points provided by the hospital. See also '*Advice to patients & carers'.*
3. **Serum creatinine should be measured 7 days after treatment initiation**. If an increase in creatinine is observed, this value should be used as the new reference baseline. A slight increase in creatinine (average 10 micromoles/L) has been observed early on in treatment; in most cases reaching a plateau after 7 days**. If an increase is observed, creatinine should be remeasured after another 7 days**. Further increases should prompt consideration of further investigation and treatment discontinuation.
4. **U&E's (including magnesium and potassium) and creatinine clearance should be monitored periodically thereafter (at least annually).**
5. **Serum LFT's should be measured 7 days after treatment initiation. Repeat LFT's at month 1, 2, 3, 4, 5, 6, 9, 12, and then periodically thereafter (at least annually).**
6. **Patients should receive regular cardiac examinations,** including an ECG and evaluation for symptoms of heart failure **at least every 6 months**. Treatment should be discontinued if the patient develops permanent AF.
7. Awareness of the potential for pulmonary toxicity and relevant lung examinations if necessary.
8. Repeat prescribing of dronedarone no sooner than one month after initiation, and once stable.
9. Inform the consultant of any changes in the patient's medical condition and/or prescribed medication, especially adverse effects. See '*Table 1: Adverse effects and other management'*
10. Provide ongoing advice on the need for contraception to female patients of childbearing age.
11. Refer the management back to the specialist if the patient becomes or plans to become pregnant.
12. Refer prescribing back to the consultant should problems arise that cannot be readily corrected.

Patient / carer responsibilities:

- After counselling, to be willing to take / administer prescribed medication as directed at home and attend regularly for monitoring and review appointments.
- To report any significant signs or symptoms relating to their condition, including side effects or concordance issues to the GP.
- Inform the specialist or GP immediately if they become pregnant or wish to become pregnant.

Table 1: Adverse effects & other management

Result	Action for primary care
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	
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.

Further support

- Medicines Information Department, Musgrove Park Hospital: 01823 342253
- Medicines Information Department, Yeovil District Hospital: 01935 384327
- Prescribing & Medicines Management Team, NHS Somerset: 01935 384123
- Medicines Management Team, Somerset NHS Foundation Trust: 01823 368265

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Approved by:	Somerset Prescribing Forum, NHS Somerset	Nov 2011
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	Drug & Therapeutics Committee, Somerset NHS FT	
	MH Drug & Therapeutics Committee, Somerset NHS FT	N/A
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References

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- NICE TA197 - Dronedarone for the treatment of non-permanent atrial fibrillation Updated Dec 2012
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- NICE NG196 Atrial fibrillation: diagnosis and management Published: 27 April 2021 Last updated: 30 June 2021 https://www.nice.org.uk/guidance/ng196/chapter/Recommendations
- MHRA Drug Safety Update - Dronedarone Dec 2014
- MULTAQ® (Dronedarone) Prescriber Guide v2.0 Oct 2021
- Multaq 400mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- Dronedarone Aristo 400mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- Specialist Pharmacy Service – Lactation Safety Information - Dronedarone https://www.sps.nhs.uk/medicines/dronedarone/
- Dronedarone monitoring – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice