Shared care protocol

Dronedarone for patients within adult services

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Version	Date published	Changes since previous version
RDTC v1.0	7th December 2023	Hyperlinks updated to link to current resources. Bepridil removed as an interacting drug (no longer marketed) Section 10: Cross reference added to contraindication if HR <50bpm

Local review and adoption

Local approval	Date
Local content added	2nd May 2024
Approved for use by Lancashire and South Cumbria ICB	9th May 2024

Clinical content has been reviewed and updated by the RDTC on the date indicated above. Every effort is made to keep the content up to date. These templates are provided to the North West and North East and Yorkshire ICBs for localisation and approval through standard ICB processes. The most recent version is available on the RDTC website at https://rdtc.nhs.uk/publication-type/shared-care/.

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Shared Care Protocol

Dronedarone for patients within adult services

1. Background	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.

2. Licensed and agreed off-label indications	Licensed indication: maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation.
	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

3. Locally agreed indications	National scoping did not identify any additional appropriate off-label indications.
4. Initiation and ongoing dose regime	Transfer of monitoring and prescribing to primary care is normally after at least 1 month, and when the patient's dose has been optimised and with satisfactory investigation results for at least 1 month. 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:** 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.
5. Baseline investigations, initial monitoring, and ongoing monitoring to be undertaken 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 the 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 (see below regarding primary care availability) • 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 6 remains appropriate.

6. Ongoing monitoring requirements to be undertaken by primary care

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.

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

7. Pharmaceutical aspects

Route of administration:	Oral
Formulation:	400 mg film-coated tablets
Administration details:	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.
Other important information:	Grapefruit juice should be avoided during treatment with dronedarone (see section 7).

8. Cautions and contraindications

This information does not replace the Summary of Product Characteristics (SPC), and should be read in conjunction with it. Please see BNF & SPC for comprehensive information.

Contraindications:

- 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 (see section 9).
- 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 (see section 9).
- Co-administration with dabigatran.
- QTc Bazett interval greater than 500 milliseconds.
- Severe hepatic or renal impairment (CrCl less than 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 (see also section 5 & section 6).

9. Significant drug interactions	The following list is not exhaustive. Please see BNF & SPC for comprehensive information and recommended management. **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 (see section 8). 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, 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).

10. Adverse effects and management

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**.** For information on incidence of ADRs see relevant SPCs.

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

Advice based on shared care guidelines published by NHS England, and checked against current guidance.

Adverse effect	Management
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 less than 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 heart rate remains >50 without symptoms.
Heart rate ≤ 50bpm or ≤ 60bpm with symptoms NB: dronedarone is contraindicated if HR less than 50bpm (see section 8).	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 greater than 5xULN or any symptoms of hepatic injury	**Stop dronedarone**. Urgent referral to initiating specialist and hepatologist.
ALT elevated greater than 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. Discontinuation may be warranted if symptoms confirmed.
Gastrointestinal disturbance: diarrhoea, nausea, vomiting, abdominal pain, dyspepsia	Continue dronedarone. May require dose reduction; discuss with specialist if persistent.

Adverse effect	Management
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.

11. Advice to patients and carers 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 drugs.	**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 broad spectrum sunscreen (at least SPF30). These measures should be continued for the duration of therapy. Patient information: British Heart Foundation – Anti-arrhythmics
12. 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. Information for healthcare professionals: UK Drugs in Lactation Advisory Service
13. Specialist contact information and arrangements for referral	The specialist team should: • make contact with the patient's GP requesting them to prescribe under a shared care agreement as soon as practicably possibly after the initial supply has been provided to the patient. Please note secondary care retains responsibility for monitoring and supply until the GP has agreed to prescribe under this shared care agreement. • Share the results of any blood monitoring with primary care. • Reassess the patient after 6 months for clinical response. • Prior to entering into a shared-care agreement, secondary care will advise the GP on frequency of monitoring, management of any dose adjustments and when to stop treatment. • Secondary care should ensure that clear backup arrangements exist for GPs to obtain advice if required.
14. Additional information	Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed. Ensure that the specialist is informed in writing of any changes to the patient's GP or their contact details.
15. References	1. British National Formulary accessed via https://bnf.nice.org.uk/ on 26/10/2023. 2. Dronedarone hydrochloride 400 mg film-coated tablets (Multaq®). Sanofi. Date of revision of the text: 01/01/21. Accessed via https://www.medicines.org.uk/emc/product/497/ on 26/10/23. 3. 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/product/10924/smpc on 26/10/23. 4. Dronedarone 400 mg film-coated tablets. Aurobindo Pharma – Milpharm Ltd. Date of revision of the text: 08/03/2022. Accessed via https://www.medicines.org.uk/emc/product/14895/smpc on 11/10/23. 5. NHS England. Items which should not routinely be prescribed in primary care: policy guidance. August 2023. Last updated October 2023. Accessed via https://www.england.nhs.uk/long-read/items-which-should-not-routinely-be-prescribed-in-primary-care-policy-guidance/ on 26/10/23. 6. 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 26/10/2023. 7. NICE. TA197: Dronedarone for the treatment of non-permanent atrial fibrillation. Last updated December 2012. Accessed via https://www.nice.org.uk/guidance/ta197 on 26/10/2023. 8. NICE. NG196: Atrial fibrillation: diagnosis and management. Last updated June 2021. Accessed via https://www.nice.org.uk/guidance/ng196 on 26/10/2023. 9. Specialist Pharmacy Service. Medicines Monitoring. Dronedarone. Published July 2021 Accessed via https://www.sps.nhs.uk/monitorings/dronedarone-monitoring/ on 26/10/2023.

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16. To be read in conjunction with the following documents	• Shared Care for Medicines Guidance – A Standard Approach (RMOC). Available from https://www.sps.nhs.uk/articles/rmoc-shared-care-guidance/ • NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/ • General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care • NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.