National shared care protocol adapted for local use:

Dronedarone for patients in adult services

As well these protocols, 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 within scope of this shared care protocol (section 2) and communicated to primary care.
- Use a shared decision making approach; 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 and document patient 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 at least 6 months and until optimised.
- Once treatment is optimised, if shared care is considered appropriate, write to the patient's GP practice and request shared care; 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, including where there are unforeseen delays to transfer of 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 woman becomes or wishes to become pregnant.
- Provide advice to primary care on the management of adverse effects if required.

Primary care responsibilities

- If shared care is not accepted, inform the specialist of the decision in writing within 14 days with reasons as to why shared care cannot be entered into.
- If accepted, prescribe ongoing treatment as detailed in the specialists request and as per section 5, taking into any account potential drug interactions in section 7.
- Adjust the dose of dronedarone 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 dronedarone and make an urgent referral to the specialist 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 and/or carer responsibilities

- 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.

1. Background

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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. Indications

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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 off-label use Back to top

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

4. Contraindications and cautions Back to top

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 7)
- 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 7)
- 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 (see also section 8 & section 9).

5. Initiation and ongoing dose regimen

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- 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 6 months.
- 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.

6. Pharmaceutical aspects

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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).

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.

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 4).
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, apixaban, rivaroxaban, edoxaban). Concomitant use with rivaroxaban is not recommended. If edoxaban is taken alongside dronedarone, the recommended dose is 30mg once daily.

8. 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 immediate future will prescribing and monitoring be transferred to primary care. Back to top

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 (if ECG monitoring not being conducted in primary care- see below)
- Chest X-ray and pulmonary function tests, if respiratory symptoms or toxicity suspected
- It is expected that patients taking dronedarone will remain under the oversight of a specialist with an annual review in a form appropriate to the clinical situation.
- 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.

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	Frequency
Urea and electrolytes (including magnesium and potassium) and creatinine clearance.	Every 6 months
Liver function tests	• At month 9 and month 12 (monthly monitoring to be undertaken by secondary care for first 6 months of treatment- see above) • Every 6 months thereafter
Symptoms of heart failure, e.g. development or worsening of weight gain, dependent oedema, or dyspnoea	Ongoing
ECG (If primary care prescribers do not feel competent to interpret the ECG, secondary care should be informed when shared care is initiated so that they can continue to monitor the patient's ECG.)	At least every six months
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 https://yellowcard.mhra.gov.uk/

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

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 significant 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.
QTc interval ≥ 500 milliseconds	**Stop dronedarone** and discuss alternative with Cardiologist.

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.

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:

- **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.

Patient information:

British Heart Foundation – Anti-arrhythmics:

https://www.bhf.org.uk/informationsupport/heart-matters-magazine/medical/drug-cabinet/anti-arrhythmics

AF association:

AFA Dronedarone - (P).indd (heartrhythmalliance.org)

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:

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:

It is not known whether dronedarone is excreted in breast milk. Specialist advice should be sought.

13. Specialist contact information

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Specialists and primary care prescribers are encouraged to communicate directly where questions arise around the shared care for a particular patient. If issues remain after these discussions, the Chief/Senior Pharmacist at the ICB or hospital Trust should be contacted for advice.

Out of hours: a consultant, specialist registrar or pharmacist may be contacted via the appropriate hospital switchboard.

NOTTINGHAM UNIVERSITY HOSPITALS switchboard 0115 924 9924

SHERWOOD FOREST HOSPITAL switchboard 01623 622515

NOTTINGHAM CITY HOSPITAL switchboard 0115 9691169

14. Additional information

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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

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16. Other relevant national guidance

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- 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/.

17. Local arrangements for referral

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Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.

- Prescribing and monitoring responsibility will only be transferred when it is agreed by the specialist and the patient's primary care prescriber that the patient is stabilised on their medication regimen without adverse effect and with benefits demonstrated.
- The specialist will request shared care with the GP in writing.
- If the GP doesn't agree to shared care, they should inform the specialist of their decision in writing within 14 days.
- In cases where shared care arrangements are not in place or where problems have arisen within the agreement and patient care may be affected, the responsibility for the patients' management including prescribing reverts to the specialist.
- Should the patient's condition change, the GP should contact the relevant specialist using the details provided with the shared care request letter.