National shared care protocol: Adapted for use as WY ICS amber guidance

Dronedarone for patients in adult services

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 communicated to patient's GP.
- 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 informed consent. Provide an appropriate patient information leaflet.
- Assess for contraindications and cautions and interactions.
- Conduct required baseline investigations and initial monitoring (see section 8).
- Initiate and optimise treatment as outlined in section 5. Prescribe the maintenance treatment for a minimum of 4 weeks.
- Once treatment is optimised, send information 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 (section 13).
- Prescribe sufficient medication to enable transfer to primary 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

- Respond to the specialist in writing within 2 weeks if unwilling to take over prescribing and monitoring as requested by specialist. Include rationale for unwilling to take over prescribing.
- If accepted, prescribe ongoing treatment as detailed in the specialist's 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

- To agree and accept responsibility for taking dronedarone as prescribed.
- To understand how to take dronedarone safely.
- To understand the duration of treatment prescribed initially by the hospital specialist.
- To understand the most common adverse events/side effects and inform the Specialist/GP as soon as reasonably possible should they occur and significantly affect the use of the medicines.
- To understand the circumstances under which the medicines should be immediately stopped and what action to take.
- To understand contents of written information provided by the Specialist and in the patient information leaflet supplied with the medicines and to seek clarification if required.
- To attend for blood tests/disease monitoring on time. Be aware that medicines may be stopped if they do not attend.
- To check with the community pharmacist that there are no interactions with dronedarone, and other medications taken including other prescribed medications, medicines bought over the counter and herbal/homoeopathic products.
- To check with dentists or other specialists who may prescribe medicines that there are no interactions with dronedarone.
- Avoid grapefruit juice while taking dronedarone.

- To contact the GP, Specialist or Medicines Information patient helpline if further information or advice is needed about this medication or if there is anything they do not understand. More information on asking about medication can be found in the Me & My Medicines Charter https://meandmymedicines.org.uk/the-charter/
- Use an appropriate form of contraception, as agreed with their doctor/nurse/sexual health service.
- Inform the specialist or primary care prescriber immediately if they become pregnant or wish to become pregnant.
- The NHS Website – NHS information on health link and medicines link

1. Background

Back to top

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 an amber guidance 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.

2. Indications

Back to top

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

Please see BNF & SPC for comprehensive information.

5. Initiation and ongoing dose regimen

Back to top

- The patient will be followed up by cardiology until their condition is stable then their care will be transferred to the GP.
- The patient can be referred back to the hospital specialist for advice or review when necessary.
- 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

Back to top

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

Back to top

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, rivaroxaban, edoxaban).

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 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.
  An increase in plasma creatinine (mean increase 10 µmol/l) can occur due to a reduction in tubular creatinine secretion with dronedarone treatment. This increase usually occurs early after treatment initiation and reaches a plateau after 7 days. If an increase in creatinine is observed after 7 days, serum creatinine should be re-measured after a further 7 days. If no further increase in creatinine is observed, this value should be used as the new reference baseline taking into account that this may be expected with dronedarone. The small rise in creatinine does not reflect a decline in renal function, therefore it should not prompt discontinuation of other drug therapies, such as ACE inhibitors or Angiotensin II Receptors Antagonists or adjustment of diuretic doses.

If serum creatinine continues to rise then consideration should be given to further investigation and discontinuing treatment.
Dronedarone therapy should only be stopped if the eGFR falls below 30ml/min; the patient should then be referred back to the initiating clinician

- Monitor concurrent medicines as appropriate, e.g. anticoagulants, digoxin.

Follow Up:

- ECG to be performed if a patient is noted to be bradycardic or presents with any other red flag symptoms such as syncope
- 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 9 remains appropriate.

Disease Monitoring:

The decision to continue therapy and response to treatment will be assessed by the hospital specialist.

9. Ongoing monitoring requirements to be undertaken by primary care

Back to top

See section 10 for further guidance on management of adverse effects/responding to monitoring results.

Monitoring	Frequency
Urea and electrolytes (including 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	to be performed if a patient is noted to be bradycardic or presents with any other red flag symptoms such as syncope

(If relevant) 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

Back to top

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 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.

11. Advice to patients and carers

Back to top

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

12. Pregnancy, paternal exposure and breast feeding

Back to top

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: https://www.sps.nhs.uk/medicines/dronedarone/

13. Specialist contact information

Back to top

See Clinic letter

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