South London
Cardiac and Stroke Network

Dronedarone for the maintenance of sinus rhythm in patients with non-permanent (paroxysmal / persistent) atrial fibrillation (AF)

The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Dronedarone must be initiated and managed by the hospital specialist team for at least the first six months of therapy. This includes taking responsibility for issuing prescriptions for dronedarone and ensuring appropriate monitoring is undertaken.

Dronedarone is an option for the maintenance of sinus rhythm in patients with paroxysmal or persistent AF and who have at least one of the following CV risk factors:

- **Age 70 years or older**
- **Hypertension requiring drugs of at least two different classes**
- **Diabetes mellitus**
- **Previous transient ischaemic attack (TIA), stroke or systemic embolism**
- **Left atrial diameter of ≥ 50 mm**

Dronedarone should only be considered for patients whose AF has not been controlled by first-line treatment and after consideration of other anti-arrhythmic therapies.

Initiation

- **Dronedarone should only be initiated by a consultant cardiologist.**
- Dronedarone should be prescribed at a dose of 400mg twice daily. No loading dose or further dose adjustments are required.
- Prescribing responsibility must remain with the initialing hospital team for ***at least*** the first six months of treatment
- The initiating hospital team is responsible for ensuring the cardiac, liver and renal monitoring is carried out in line with the recommendations overleaf. The results should be communicated to the GP.
- A follow-up ECG should be arranged by secondary care within 7-10 days of initiation for selected patients. This includes patients at risk of QT prolongation, for example, due to concomitant prescription of other drugs which may prolong the QT interval, those switched from amiodarone to dronedarone therapy and those prescribed concomitant beta-blockers or rate controlling calcium channel blockers (verapamil / diltiazem).

Contra-indications	Cautions
• Hypersensitivity to dronedarone or excipients • History of, or current, heart failure; or with left ventricular systolic dysfunction (ejection fraction < 40%) • Permanent AF • Liver or lung toxicity related to previous use of amiodarone • Second or third-degree AV block or sick sinus syndrome (unless in combination with a pacemaker) • Bradycardia < 50bpm • QTc Bazett interval > 500milliseconds • Patients with haemodynamic instability • Severe hepatic impairment or severe renal impairment (eGFR<30ml/min) • Pregnancy and breast feeding	• Electrolyte imbalance – correct hypokalaemia and hypomagnesaemia before initiation • The co administration of dronedarone with any drugs that prolong the QT interval. Please check www.qtdrugs.org for details. • Women of child-bearing age – ensure appropriate contraception
Drug interactions: See overleaf for details of drug interactions including contraindicated drug therapies	

On-going supplies

The initiating hospital team is responsible for prescribing dronedarone for at least the first six months of therapy and for ensuring that the appropriate safety monitoring is carried out.

Transfer of prescribing responsibility

The transfer of prescribing and monitoring responsibility to the general practitioner should only be considered after the initial six month period, when the patient is stable on dronedarone with no evidence of cardiac or hepatic toxicity; and ONLY where the GP agrees to take over the on-going prescribing and monitoring of the drug.

Side effects - *See BNF for full details*

The most common adverse effects of dronedarone are gastrointestinal, including diarrhoea, nausea and vomiting, abdominal pain and dyspepsia. Other commonly occurring side effects include bradycardia, rashes and pruritis, fatigue and asthenia. Rare dermatological side effects include erythema, eczema, photosensitivity and allergic dermatitis. Abnormalities of taste have also been reported.

Onset of dyspnoea or a non-productive cough may be related to pulmonary toxicity. If pulmonary toxicity is suspected, relevant pulmonary examinations should be undertaken and treatment discontinued if toxicity is confirmed.

Dronedarone is a black triangle drug. Any adverse effects must be reported to the Committee on Safety of Medicines (CSM).

Monitoring

Cardiac effects

It is the responsibility of the specialist team to ensure patients initiated on dronedarone have an ECG at baseline and then at six monthly intervals throughout therapy to confirm sinus rhythm is maintained. If AF recurs during therapy, consider cessation of dronedarone. If permanent AF develops during treatment, dronedarone should be discontinued. Patients initiated on dronedarone should be advised to consult a physician if they develop or experience worsening signs or symptoms of heart failure, such as weight gain, dependent oedema, or increased dyspnoea. If heart failure develops, consider suspending or discontinuing dronedarone and refer back to the initiating clinician.

Hepatic effects

Patients initiated on dronedarone should have liver function tests (LFTs) carried out one week after initiation of therapy; then monthly for the first six months of treatment, at 9 and 12 months and then at least annually thereafter**. If alanine transaminase (ALT) levels become elevated to ≥3× upper limit of normal (ULN) (approximately 150iu/L), levels should be retested within 48–72 hours. If ALT levels are confirmed to be ≥3× ULN after retesting, dronedarone treatment should be withdrawn and the patient reviewed urgently by the hospital team.**

Renal effects

A small increase in serum creatinine of approximately 10micromol/L is expected after initiation of dronedarone. Renal function (serum creatinine level) should be checked one week after initiation. If the creatinine level has risen, this should be documented as the new baseline value for the patient. The rise in creatinine is due to a reduction in tubular creatinine secretion and does not reflect a decline in renal function, therefore it should not prompt discontinuation of other drug therapies, such as ACE inhibitors or ARBs or adjustment of diuretic doses. Dronedarone therapy should only be stopped if the eGFR falls below 30ml/min; the patient should then be referred back to the initiating clinician.

Summary of monitoring requirements for dronedarone

LFTs	Serum creatinine	ECG
• At baseline • Day seven • Monthly for six months • Month nine • Month 12 • Annually throughout therapy	• At baseline • Day seven (to reset baseline) • Annually throughout therapy	• At baseline • Month six • Six monthly throughout therapy

Drug interactions – *Please see BNF for full details*

Interacting drug / drug class	Details and action to be taken
Anti-epileptic drugs	Concomitant use of phenobarbitone, carbamazepine and phenytoin is not recommended
Azole anti-fungals	Concomitant use of ketoconazole, itraconazole, voriconazole, pozaconazole is contraindicated (not topical preparations)
Beta-blockers	Increased risk of bradycardia. Beta-blockers should be initiated at low dose and up-titrated only after ECG assessment. For patients on a beta-blocker at the time of initiation of dronedarone, an ECG should be performed and the dose of beta-blockers adjusted if needed. In addition, dronedarone increases plasma levels of metoprolol and propanolol
Calcium channel blockers: verapamil / diltiazem	Caution in use - risk of bradycardia with concomitant use. Initiate the calcium channel blocker at a low dose and increase dose only after ECG assessment. For patients on verapamil / diltiazem at the time of initiation of dronedarone, an ECG should be performed and the dose of calcium channel blockers adjusted if needed
Digoxin	Dronedarone increases plasma digoxin levels. In patients taking digoxin at the time of initiation of dronedarone, the digoxin dose should be reduced by 50%, serum digoxin levels should be monitored and ECG assessment considered.
Drugs that prolong QT interval	The co administration of dronedarone with any drugs that prolong the QT interval. Please check www.qtdrugs.org for details.
Grapefruit juice	Ingestion of grapefruit significantly increases dronedarone levels. Patients should be advised to avoid drinking grapefruit juice throughout dronedarone therapy
Immunosuppressants: tacrolimus, sirolimus	Dronedarone may increase levels of tacrolimus and sirolimus. Monitoring of plasma levels with dose adjustments should be undertaken
Macrolide antibiotics	Concomitant use of telithromycin, clarithromycin and erythromycin is contraindicated
Nefazadone	Concomitant use is contraindicated
Rifampicin	Concomitant use is not recommended
Ritonavir	Concomitant use is contraindicated
St John's wort	Concomitant use is contraindicated. Patients should be advised not to take over the counter preparations
Statins	Dronedarone may increase statin levels. It is recommended that statins are initiated at low dose and doses increased cautiously. Patients taking statins and dronedarone should be monitored for signs of muscle toxicity
Warfarin	Increased anticoagulant effect

References

- NICE TA 197 (2010): Dronedarone for the treatment of non-permanent Atrial Fibrillation. Accessed Oct 21st at http://guidance.nice.org.uk/TA197
- SPC Multaq® (Dronedarone) Sanofi-Aventis 2011 Accessed Oct 26th t at http://www.medicines.org.uk/emc/medicine/22894/SPC/Multaq+400mg+tablets/
- MHRA Drug Safety Update Oct 2011 Vol 5 Issue 3. Accessed Oct 26th 2011 at http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON131928