Dronedarone

Traffic light classification- Amber 1
Information sheet for Primary Care Prescribers

Licensed Indications
The maintenance of sinus rhythm after successful cardioversion in adult clinically stable adult patients with paroxysmal or persistent atrial fibrillation (AF).

Medicines Initiation
Dronedarone will be initiated by a cardiology specialist. Prescribing responsibility will remain with secondary care for 1 year from initiation.

Products available
Multaq® 400mg tablets

Dosages and route of administration
The recommended dose is 400 mg twice a day. It should be taken as one tablet with the morning meal and one tablet with the evening meal.

Duration of treatment
Treatment is potentially lifelong.

Monitoring Requirements and Responsibilities
The Cardiologist will be responsible for the monitoring required in the first year of treatment.

Ongoing monitoring in Primary Care

Frequency of Monitoring	Tests to be done		
	ECG*	LFTs	Renal Function
6-monthly	✓		
Annually		✓	✓

*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.

These are minimum requirements and may need to be performed more frequently if the patient's condition changes.

Renal and liver function will need repeating more frequently if CKD or hepatic impairment.

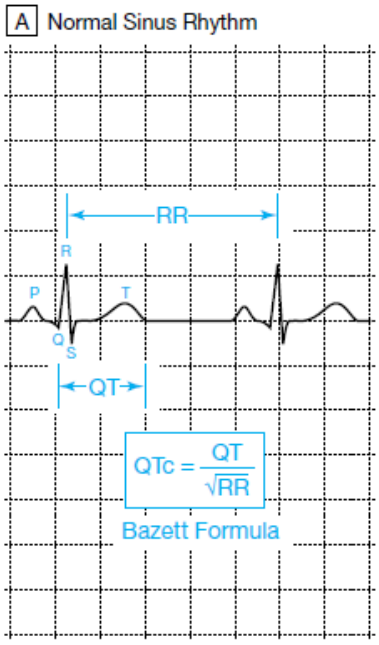
Explicit criteria for review and discontinuation of the medicine

Side effect	Action to be taken
Recurrence of AF	If permanent AF develops dronedarone should be discontinued and alternative treatment discussed with Cardiologist.
QTc interval ≥ 500 milliseconds**	Discontinue dronedarone and discuss alternative with Cardiologist.
Significant reduction in renal function	If calculated Creatinine Clearance drops to < 30ml/min (see below), discontinue dronedarone and discuss alternative treatment with Cardiologist.
Development of heart failure of left ventricular systolic dysfunction	Discontinue dronedarone and discuss alternative treatment with Cardiologist.
Alanine aminotransferase (ALT) levels ≥3 × upper limit of normal (ULN)	ALT levels should be re-measured within 48 to 72 hours. If ALT levels are confirmed to be ≥3 × ULN, treatment with dronedarone should be withdrawn and alternative treatment discussed with Cardiologist.
Development of pulmonary toxicity	Discuss with Cardiologist and refer to Respiratory Specialist
Development of hypokalaemia or hypomagnesaemia	Correct with potassium or magnesium supplements

eGFR may be considered roughly equivalent to CrCl, but if the patient is elderly, or if the eGFR is borderline, the Creatinine Clearance should be calculated using the Cockroft-Gault equation for Creatinine Clearance (ml/min):

$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine (micromol/l)}} \times 1.04 \text{ (female) or } 1.23 \text{ (male)}$$

**Most ECG machines will give an automated reading of the QT and QTc (corrected QT) interval, but for manual calculation, see below:



The Bazett formula is used to correct the QT interval for the heart rate

Contraindications

- Hypersensitivity to the active substance or to 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 <50 beats per minute (bpm)
- Permanent AF with an AF duration ≥6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician
- Patients in unstable hemodynamic conditions,
- History of, or current heart failure or left ventricular systolic dysfunction
- Patients with liver and lung toxicity related to the previous use of amiodarone
- QTc Bazett interval ≥500 milliseconds
- Severe hepatic impairment
- Severe renal impairment (CrCl <30 ml/min)
- Dronedarone is not recommended during pregnancy, in women of child bearing potential not using contraception or in breastfeeding mothers.

Precautions

- Coronary artery disease
- Elderly patients ≥75 years with multiple co-morbidities
- Patient with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take dronedarone due to the presence of lactose.

Clinically relevant medicine interactions and their management

- Potent cytochrome P450 (CYP) 3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir - co-administration is contraindicated.
- Medicinal products inducing torsades de pointes such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, terfenadine and certain oral macrolides (such as erythromycin), Class I and III antiarrhythmics - co-administration is contraindicated.
- Dabigatran plasma concentration is significantly increased by dronedarone - co-administration is contraindicated.
- Digoxin - plasma concentration increased by dronedarone - digoxin dose should be halved and clinical, ECG and plasma level monitoring is recommended.
- Beta-blockers and calcium antagonists with depressant effect on sinus and atrio-ventricular node - use with caution. Initiate at low dose and titrate after ECG assessment.
- Potent CYP 3A4 inducers such as rifampicin, phenobarbital, carbamazepine, phenytoin or St John's Wort - avoid due to decreased dronedarone exposure.

- Statins should be used with caution. Lower starting dose and maintenance doses of statins should be considered and patients monitored for clinical signs of muscular toxicity.
- Immunosupressants (tacrolimus, sirolimus, everolimus and ciclosporin). Dronedarone may increase plasma concentrations - monitor.
- Warfarin - clinically significant INR elevations (≥5) usually within 1 week after starting dronedarone were reported in patients taking oral anticoagulants. Consequently, INR should be closely monitored after initiating dronedarone in patients taking vitamin K antagonists
- Grapefruit juice increases dronedarone exposure - patients should avoid grapefruit juice beverages
- *MAO inhibitors* might decrease the clearance of the active metabolite of dronedarone and should therefore be used with caution.

Information given to patient

A patient information leaflet is available from the AF association.

Patients should be advised to consult their GP if they develop or experience signs or symptoms of heart failure, such as weight gain, dependent oedema, or increased dyspnoea or symptoms of pulmonary toxicity such as onset of dyspnoea or non-productive cough.

Patients should be advised to seek immediate advice from their GP if any symptoms of potential liver injury develop (such as sustained new-onset abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine or itching).

Patients should be warned to avoid grapefruit juice beverages while taking dronedarone.

Patient's Role

- To attend appointments for regular blood tests and 6-monthly ECG.
- To report side effects as above.

References

Multaq Summary of Product Characteristics. Last updated on www.emc.medicines.org.uk 03/10/2014
NICE TA197: Dronedarone for the treatment of non-permanent Atrial Fribrillation. Re-issued December 2012
UKMI Suggestions for Drug Monitoring in Adults in Primary Care. October 2017
NICE CG 180: Atrial fibrillation: the management of atrial fibrillation, last updated August 2014
MHRA Drug Safety Update Dronedarone (Multaq▼): cardiovascular, hepatic and pulmonary adverse events – new restrictions and monitoring requirements, 2011
Al-Khatib SM et al. What clinicians should know about the QT interval. JAMA 2003:289 (16); 2120-2127