SHARED CARE GUIDELINE
DRONEDARONE

Implementation Date: September 2020 **Review Date: September 2023**

This guidance has been prepared and approved for use within Sunderland and South Tyneside in consultation within the CCGs, and Secondary Care Trust.

The guideline sets out the details of the transfer of prescribing and respective responsibilities of GPs and specialist services within shared care prescribing arrangements. It is intended to provide sufficient information to allow GPs to prescribe this treatment within a shared care setting

Approved by:

Committee	Date
South Tyneside and Sunderland Area Prescribing Committee	August 2020

Instructions for completion:

- ☐ **Consultant to counsel patient on medication and ensure patient has been provided with information leaflet**
- ☐ **Consultant to ensure all clinical details completed on this document**
- ☐ **Consultant to ensure patient understands proposed monitoring and prescribing arrangements if a shared care agreement is entered into**
- ☐ **GP to complete final section of form and return to specialist prescriber within 28 days**
- ☐ **GP to retain copy of document on patient record within surgery**

SHARED CARE GUIDELINE					
Non-proprietary name	**DRONEDARONE**	**Brand name:**	Multaq®, also available as generic		
Dosage form and strength	400mg tablets	**Licensed Y/N?**	Yes	**BNF Class**	2.1
Indication	**Maintenance of sinus rhythm after cardioversion in clinically stable patients with paroxysmal or persistent atrial fibrillation, when alternative treatments are unsuitable (initiated under specialist supervision)** NICE TA197 (December 2012): Dronedarone is as an option for the maintenance of sinus rhythm after successful cardioversion in paroxysmal or persistent atrial fibrillation (AF) which is not controlled by first line therapy (usually including beta-blockers), and after alternative options have been considered in patients who have at least one of the following cardiovascular risk factors: • Hypertension requiring medicines of at least two different classes • Diabetes mellitus • Previous transient ischaemic attack, stroke or systemic embolism • Left atrial diameter of 50mm or greater, or • Age 70 years or older **Contraindications include patients who have left ventricular systolic dysfunction and those who have a history of, or current, heart failure. See contraindications section below.**				
Dosage and administration	400mg twice daily orally, with breakfast and evening meal. Do not take with grapefruit juice. Duration of treatment is usually indefinite (as long as treatment is considered appropriate by specialist)				
Eligibility criteria for shared care	Patients **must** be under the ***continuing care of*** **and regular review** by a consultant cardiologist. Must have a diagnosis consistent with the indication outlined above.				
Excluded patients	Patients with a contraindication to dronedarone *(see section below)*				

Initiation

Dronedarone is only suitable for prescribing in primary care following specialist initiation.

Identify baseline renal and hepatic function to initiation of dronedarone to confirm absence of severe renal and hepatic failure.

Confirm absence of any contraindications to dronedarone therapy

The primary care clinician should only be asked to prescribe the maintenance dose once the patient has been stabilised and the initial monitoring tests have been completed as outlined below.

Prescribing and monitoring responsibility must only be transferred to a GP by a cardiologist where a GP agrees to take on these responsibilities.

Monitoring to be undertaken by specialist

SUMMARY OF DRONEDARONE MONITORING

MONITORING IS TO BE UNDERTAKEN IN SECONDARY CARE UNTIL THE GP HAS AGREED TO CONTINUE MONITORING IN PRIMARY CARE

SPECIALIST RESPONSIBILITIES

(Responsible for baseline and FIRST MONTH of monitoring (and until GP has agreed to take on monitoring responsibilities)

What to monitor		Rationale	Baseline	7 days	*(*14 days)*	12 months
ECG		To check if the patient remains in sinus rhythm. Monitor for reversion back to AF. Monitor for QTc (Bazett) interval prolongation.	✓			✓
U&Es	**K+** / **Mg^{2+}**	Deficiencies in electrolytes may precipitate arrhythmias – correct & recheck if necessary	✓	✓		
Serum creatinine		An increase in creatinine has been observed usually early after initiation and reaches plateau at 7 days (consider to be new baseline Cr). If continues to rise, discontinuation may be required.	✓	✓	***Only if a change in renal function noted at the 7 day check***	
LFTS	**ALT**	If alanine transaminase (ALT) levels are elevated to > 3 x upper limit of normal (ULN), levels should be retested within 48 to 72 hours. If ALT levels are confirmed to be > 3 x ULN after retesting, dronedarone treatment should be withdrawn.	✓	✓		
Check for drug interactions		Dronedarone is primarily metabolised via the CYP3A4 isoenzyme, therefore inhibitors and inducers have the potential to cause many drug interactions.	Repeat if new agents added to patients usual prescription		See info in specific drug interaction section for further details.	
Check for adverse effects		Dronedarone has been associated with cardiovascular, hepatic and pulmonary adverse events.			See adverse effects section	

Monitoring to be undertaken by primary care

GP RESPONSIBILITIES

(assuming monitoring responsibility for patient only after baseline monitoring has been completed by specialist)

What to monitor		Rationale	Every month for first 6 months	At 6 months	At 9 months	At 12 months Then every 6 months thereafter	Action if out of range or irregular
ECG		Monitor for QTc (Bazett) interval prolongation. To check if the patient remains in sinus rhythm. Monitor for reversion back to AF.		✓		✓	If QTc ≥ 500ms – **refer urgently to initiating specialist.** **If reverted to AF – refer to initiating specialist** Urgent ECG indicated if heart rate ≤50 bpm or symptoms are present. If the patient has syncope or second or third degree heart block, admission is advised. **Any queries regarding ECG interpretation (e.g. in determining QTc), should be referred for advice to the named cardiologist for that individual patient.**
U&Es	**K+**	Deficiencies in electrolytes may precipitate arrhythmias		✓		✓	Correct electrolyte imbalance and re-check U&Es
	Mg+			✓		✓	
Serum creatinine		Periodic monitoring of renal function is required.		✓		✓	
LFTs	**ALT**	If alanine transaminase (ALT) levels are elevated to > 3 x upper limit of normal (ULN), levels should be retested within 48 to 72 hours. If ALT levels are confirmed to be > 3 x ULN after retesting, dronedarone treatment should be withdrawn.	✓	✓	✓	✓	If alanine transaminase (ALT) levels are elevated to > 3 x upper limit of normal (ULN), levels should be retested within 48 to 72 hours. If ALT levels are confirmed to be ≥ 3 x ULN after retesting, dronedarone treatment should be withdrawn & refer to initiating specialist.
Check for drug interactions		Dronedarone is primarily metabolised via the CYP3A4 isoenzyme, therefore inhibitors and inducers have the potential to cause many drug interactions.	Repeat if new agents added to patients usual prescription				See info in specific drug interaction section for further details.
Check for adverse effects		Dronedarone has been associated with cardiovascular, hepatic and pulmonary adverse events.					See adverse effects section for advice

Specialist Responsibilities	i. To initiate dronedarone in appropriate patients in accordance with licensed indications ii. To confirm the patient has no contra-indications to treatment and consider the relevance of any cautions. iii. Perform baseline liver function tests (LFTs) and check renal function before initiating treatment with dronedarone as per MHRA advice. Arrange for these blood tests to be repeated after 7 days of treatment, with a further check on renal function after 14 days of treatment if a change has been noted at the 7 day check. iv. To ensure that the patient has an adequate supply of medication (usually 28 days) until shared care arrangements are in place. Further prescriptions will be issued if, for unseen reasons, arrangements for shared care are not in place at the end of 28 days. Patients should not be put in a position where there are unsure where to obtain supplies of their medication. v. To contact the patient's GP to request agreement to prescribing under shared care; to provide a copy of this shared care agreement for their consideration and **not to transfer prescribing responsibility until the GP has formally agreed to share care in this way. Note that the initial monitoring for the first month of treatment remains the responsibility of the specialist.** vi. To discuss the benefits, limitations, monitoring requirements, adverse effects (including actions to take if adverse effects are suspected) and obtained informed consent. Advise women of child bearing age to use reliable contraceptive methods whilst taking dronedarone and for one month after stopping treatment. vii. To address any concerns with the GP regarding the patient's treatment and provide advice and support where needed. viii. To review the patient annually to assess treatment response and disease progression. ix. To communicate promptly with the GP when treatment is changed / stopped or needs to be changed / stopped by the GP, and any results of monitoring undertaken. x. To discontinue dronedarone if permanent atrial fibrillation occurs or if the patient develops any of the conditions that would lead to a contraindication. To consider discontinuation if atrial fibrillation reoccurs.
Primary Care Responsibilities	i. **Primary care clinicians should never initiate dronedarone** ii. **Reply to the specialist's request for shared care as soon as practical (within 28 days).** iii. Care must not be transferred to the GP in the first month of treatment. iv. If prescribing responsibility is accepted, provide follow up prescriptions for dronedarone at the dose advised by the secondary care specialist and ensure continuous prescribing remains clinically appropriate. v. **Ensure that the patient is receiving continuing regular reviews by a tertiary centre and/or local cardiologist. If this is not the case, dronedarone treatment should be discontinued.** vi. Primary care is responsible for the ongoing routine monitoring after the first month and onwards as outlined above vii. Due to the potential for significant drug-drug interactions, the primary care clinician must ensure there are no interactions and contra-indications with any other medications initiated in primary care. viii. To identify adverse events if the patient presents with any signs and liaise with the hospital specialist where necessary. In particular, to urgently review patients on dronedarone presenting with increasing dyspnoea or non-productive cough. ix. To report adverse events to the specialist and where appropriate to the Commission on Human Medicines/MHRA (Yellow card scheme) x. Refer to the specialist if the patient's condition deteriorates. xi. Stop treatment on the advice of the specialist or immediately if any urgent need to stop treatment arise. xii. Notify consultant if treatment with dronedarone is discontinued

Adverse effects

Adverse effect	Frequency	Investigation & Diagnosis	Action
Congestive heart failure	Very common	History & examination	Patients should be carefully evaluated for, and advised to consult a physician if they develop or experience signs or symptoms of heart failure, such as weight gain, dependent oedema, or increased dyspnoea. If left ventricular systolic dysfunction develops, treatment with dronedarone should be discontinued on discussion with initiating cardiologist.
Bradycardia	Common	Examination, ECG	Urgent ECG if heart rate <50 or symptoms are present. If the patient has syncope or second or third degree heart block, admission is advised.
QTc interval prolongation	Very common	ECG	Dronedarone may induce a moderate QTc Bazett prolongation (about 10 ms), related to prolonged repolarisation. These changes are linked to the therapeutic effect of dronedarone and do not reflect toxicity. Follow up, including ECG, is recommended during treatment. **If QTc Bazett interval is ≥500 milliseconds, dronedarone should be stopped – refer urgently to initiating cardiologist.** **Any queries regarding ECG interpretation should be directed to the named cardiologist responsible for the individual patient's care.**

	Liver function test abnormalities	Common	Serum transaminases	Patients should immediately report any symptoms of potential liver injury (such as sustained new-onset abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine or itching) to their physician. If alanine aminotransferase (ALT) levels are elevated ≥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 - refer urgently to initiating cardiologist**. Appropriate investigation and close observation of patients should continue until normalisation of ALT.
	Acute liver disorders	Rare		
	Pulmonary toxicity *(suggested by new or worsening cough and/or shortness of breath)*	Uncommon	Prompt CXR and ECG to exclude alternative diagnoses	If pulmonary toxicity is suspected, refer urgently to initiating cardiologist/specialist or to a respiratory physician for confirmation of diagnosis and consideration of alternative anti-arrhythmics. Acute admission may be required. Early investigation with HRCT chest scan is important. **Ask about breathlessness and non-productive cough, relating to possible pulmonary toxicity, at each review visit.**
	Gastrointestinal: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain	Common	History & examination	If persistent or problematic, discuss with initiating cardiologist.
	Taste disturbances	Common - dysguesia / Rare- ageusia		
	Skin disorders: **Rashes (generalised, macular, maculo-papular), pruritis**	Common		
	Erythemas, eczema, dermatitis, photosensitive reaction	Uncommon		
	Vasculitis	Rare		
	Anaphylactic reactions including angioedema	Rare	Clinical examination	Acute admission may be required.
	Frequency definitions: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100); Rare (≥1/10 000 to <1/1000); Very rare (<1/10 000) **For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult SPC or BNF.**			
Precautions	Careful monitoring during dronedarone administration is recommended by regular assessment of cardiac, hepatic and pulmonary function *(see monitoring section)*. If AF reoccurs, discontinuation of dronedarone should be considered. Treatment with dronedarone should be stopped during the course of treatment, in case the patient develops any of the conditions which would lead to a contraindication *(see contraindications section)* Monitoring of co-administered medicinal products like digoxin and anti-coagulants is necessary *(see interaction section)* Dronedarone is not recommended in breastfeeding mothers			

<table>
<tr><td>Contraindications</td><td>

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 haemodynamic 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
Co-administration with potent cytochrome P450 (CYP) 3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir
Co-administration with medicinal products inducing torsades de pointes such as phenothiazines, tricyclic antidepressants, terfenadine, oral macrolides, Class I and III antiarrhythmics
QTc Bazett interval ≥500 milliseconds
Severe hepatic impairment
Severe renal impairment (CrCl <30 ml/min)
Co-administration with dabigatran
Pregnancy and in women of child-bearing potential not using contraception

</td></tr>
<tr><td rowspan="8">Common Drug Interactions</td><td colspan="2">COMMON DRUG INTERACTIONS</td></tr>
<tr><td colspan="2">Dronedarone is primarily metabolised by CYP3A4. Therefore, inhibitors and inducers of CYP 3A4 have the potential to interact on dronedarone.

(Note: this list is not exhaustive; for a full list and details of interactions, please refer to BNF and SPC. For further information on drugs that affect the QT interval, see the Credible Meds website).</td></tr>
<tr><td>Grapefruit juice</td><td>Grapefruit juice is a CYP 3A4 inhibitor that increases dronedarone exposure, therefore patients should be advised to avoid while taking dronedarone.</td></tr>
<tr><td>Potent CYP3A4 inhibitors</td><td>Drugs that inhibit CYP3A4 may increase serum concentration of dronedarone with the potential for toxicity.

Co-administration with ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir is contraindicated. Caution should be taken with the moderate/weak CYP3A4 inhibitors – erythromycin and the calcium channel blockers (verapamil and diltiazem – see below entries for more details)</td></tr>
<tr><td>Potent CYP3A4 inducers</td><td>Co-administration with potent CYP3A4 inducers (e.g. rifampicin, phenobarbital, carbamazepine) decrease dronedarone exposure and is not recommended</td></tr>
<tr><td>Digoxin</td><td>Dronedarone increases plasma levels of digoxin and has potential to interact with dronedarone from a pharmacodynamic perspective, and thus may precipitate the symptoms and signs of digoxin toxicity. A synergistic effect on heart rate and atrio-ventricular conduction is possible.
If concurrent use is indicated, the digoxin dose should be reduced by approximately 50%, serum levels of digoxin should be closely monitored and ECG monitoring is recommended.</td></tr>
<tr><td>Warfarin</td><td>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.</td></tr>
<tr><td>Direct oral anticoagulants (DOACs)</td><td>Dabigatran: Co-administration is contraindicated.
Rivaroxaban: dronedarone is likely to increase the exposure of dronedarone and my increase bleeding risk therefore, concurrent use is not recommended.
Apixaban: dronedarone may increase the exposure of apixaban. However, no dose adjustment for apixaban is required when co-administered with dronedarone.
Edoxaban: edoxaban exposure is increased - see SPC for dose adjustment when used concomitantly with dronedarone</td></tr>
<tr><td>Beta-blockers</td><td>Sotalol must be stopped before starting dronedarone.

Other beta-blockers should be used with caution concomitantly with dronedarone: beta-blockers should be initiated at a low dose and up-titration should be done only after ECG assessment. In patients already</td></tr>
</table>

		taking beta-blockers at time of dronedarone initiation, an ECG should be performed and the beta-blocker dose should be adjusted if needed.
	Calcium-channel blockers (diltiazem or verapamil)	Calcium channel blockers with depressant effects on sinus and atrio-ventricular node such as verapamil and diltiazem should be co-administered with caution with dronedarone. In patients on dronedarone, they should be initiated at low dose and up-titration should be done only after ECG assessment. In patients, already on diltiazem or verapamil at time of dronedarone initiation, an ECG should be performed and the calcium channel blocker dose adjusted if needed.
	Drugs inducing torsades de pointes	Medicinal products inducing torsades de pointes such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, certain oral macrolides (such as erythromycin), terfenadine and Class I and III antiarrhythmics are contraindicated because of the potential risk of proarrhythmia.
	Statins	Statins should be used with caution. Lower starting dose and maintenance doses of statins should be considered and patients monitored for clinical signs of toxicity.
	St John's Wort	Co-administration is not recommended as St John's Wort may decrease dronedarone exposure
	MAO inhibitors	MAO inhibitors may decrease clearance of the active metabolite of dronedarone and should be used with caution.
Communication/ Contact Details	*Contact details of responsible consultant to be provided on shared care request referral form* *For urgent enquiries out of hours: on call cardiologist via hospital switchboard: 0191 5656256*	

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to full prescribing data in the SPC or the BNF.

Private and Confidential
Dronedarone
Shared Care Request/Confirmation

Patient information:
To be completed by specialist prescriber:

Consultant ……	**Patient details (use hospital label if preferred)**
Department ……	**Name** ……
Hospital ……	**Address** ……
	……
	Postcode …… **Sex** ……
	NHS or Hosp. Reg. No. …… **DoB** ……

Treatment Requested for Prescribing in Accordance with Shared Care Arrangement:
To be completed by specialist prescriber:

Drug name	
Dose	
Frequency	
Indication	
Other information	

Name (print) ……

Position: ……..

Signature (of specialist prescriber) …… Date ……..

Acceptance/rejection of treatment under Shared Care Agreement:

To be completed by GP:

Please tick one box

I ACCEPT the proposed shared care arrangement for this patient ❑

Or

I ACCEPT the proposed shared care arrangement with the caveats below ❑

Or

I DO NOT ACCEPT the proposed shared care arrangement for this patient ❑

My caveats / reason(s) for not accepting include: ……
……

Name (print)…….. Signature (of GP)…….. Date……

N.B. Participation in this shared care arrangement implies that prescribing responsibility is shared between the specialist prescriber and the patient's GP