BNSSG Shared Care Guidance
Please complete all sections

Section 1: Heading

Drug	Dronedarone (Multaq®) 400mg film-coated tablets
Amber ***three months***	

Indication	Dronedarone is indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically-stable patients with paroxysmal or persistent atrial fibrillation (AF). Due to its safety profile, dronedarone should only be prescribed after alternative treatment options have been considered. To be started only on advice of a cardiologist. Dronedarone is contraindicated in patients with permanent AF who will not or cannot be cardioverted to normal sinus rhythm.
	
	Dronedarone is an option only in people:
	- 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 dimaeter of 50mm or greater or
	  - age 70 years or older
	- Who do not have left ventricular systolic dysfunction and
	- Who do not have a history of, or current, heart failure
	
	Patients who do not meet the criteria above who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Speciality / Department	Cardiology
Trust(s)	University Hospitals Bristol NHS Foundation Trust
	North Bristol NHS Trust
	Weston Area Health NHS Trust

Section 2: Treatment Schedule

Usual dose and frequency of administration	400mg twice daily; one tablet with morning meal and one tablet with evening meal

Route and formulation	Oral, film-coated tablets
Duration of treatment	Maintenance treatment, to be continued as long as tolerated and required on instruction of cardiologist

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist.

Baseline tests - where appropriate
Electrocardiogram to ensure sinus rhythm Echocardiogram (ECG) to assess for heart failure or left ventricular systolic dysfunction Urea and electrolytes to measure renal function; contraindicated if CrCl <30mL/min Liver function tests; contraindicated if severe hepatic impairment Potassium and magnesium levels; with correction of deficiency if needed
Subsequent tests - where appropriate
1. ECG every 6 months to ensure maintenance of sinus rhythm. Dronedarone should be discontinued if the patient develops bradycardia <50bpm, second- or third- degree atrioventricular block, complete bundle branch block, distal block, sinus node dysfunction, atrial conduction defects or sick sinus syndrome (unless pacemaker in situ); or if permanent AF and no longer for consideration by the physician to restore sinus rhythm; to monitor QTc interval as contraindicated if ≥ 500 milliseconds, would expect to see a rise of approximately 10 milliseconds during treatment 2. LFTs one week after initiation, then monthly for 6 months, at 9 months, at 12 months then periodically thereafter – if alanine aminotransferase (ALT) levels are elevated to ≥ 3 times upper limit of normal, repeat after 48 to 72 hours, if confirmed then dronedarone should be withdrawn. 3. U&Es one week after initiation; may see mean increase of 10micromol/L in serum creatinine, following initiation of treatment, and reaching a plateau at 7 days. If a rise is seen, repeat U&Es at 7 days to see if creatinine increase plateaus. If larger increases seen or if this continues to rise, further investigation and consideration to discontinue treatment is appropriate 4. Potassium and magnesium levels as appropriate depending on the patient and their other conditions: with correction of deficiency as needed 5. If pulmonary toxicity is suspected e.g. new onset dyspnoea or non-productive cough, relevant lung examinations should be considered and treatment discontinued if confirmed

Section 4: Side Effects

Please list the most common side effects and management. Please provide guidance on when the GP should refer back to the specialist.

Side effects and management	Rare side effects (≥1/10,000 to <1/1000) - Anaphylactic reactions including angioedema - Aguesia - Vasculitis including leukocytoclastic vasculitis - Hepatocellular liver injury including life-threatening acute liver failure Uncommon side effects (≥1/1,000 to <1/100) - Dysguesia - Interstitial lung disease including pneumonitis and pulmonary fibrosis - Erythema, rash erythematous

	- Eczema - Photosensitivity reactions - Allergic dermatitis, dermatitis Common side effects (≥1/100 to <1/10) - Bradycardia - Diarrhoea, vomiting, nausea - Abdominal pain, dyspepsia Very common side effects (≥1/10) - Congestive heart failure - Increase in blood creatinine ≥10% five days after initiations - QTc prolongation >450msec in male, >470msec in female
Referral back to specialist	Side effects or adverse reactions warranting premature termination of treatment; particularly if associated with derangement of liver function, worsening respiratory function, creatinine rises that have not plateaued, hypersensitivity reactions, ECG changes as described, new or worsening heart failure

Section 5: Drug Interactions

Please list clinically significant drug interactions (eMC link please click here)

Significant Drug Interactions	Dronedarone is primarily metabolised by CYP 3A4 Dronedarone is a moderate inhibitor of CYP 3A4, a mild inhibitor of CYP 2D6 and a potent inhibitor of P-glycoproteins Dronedarone and/or its metabolites have been shown to inhibit transport proteins e.g. Organic Anion Transporters (OATs) and Organic Cation Transporters (OCTs) Drugs inducing Torsades de pointes are contraindicated due to potential risk of proarrhythmia; such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, macrolides e.g. erythromycin, terfenadine, Class I antiarrhythmics, Class III anti-arrhythmics Potent CYP 3A4 inhibitors increase exposure to dronedarone and are contraindicated with dronedarone; examples include triazole antifungals, ritonavir, telithromycin, clarithromycin or nefazodone Combination of dronedarone with diltiazem and verapamil can lead to sinus- or atrio-ventricular node depression thus ECG and heart rate should be monitored at initiation and at dose changes Plasma digoxin concentration will increase when prescribed with dronedarone, precipitating signs and symptoms of digoxin toxicity. Clinical, ECG and biological monitoring is recommended, and the digoxin dose should be halved. Clinically-significant INR elevations of ≥5 have been seen within 1 week after starting dronedarone, close monitoring is recommended at initiation and with dose changes, in patients taking vitamin K antagonists Dronedarone has been shown to significantly increase dabigatran levels, co-administration is contraindicated Dronedarone in combination with beta-blockers increase the incidence of bradycardia; sotalol must be stopped before starting dronedarone and action should be taken when using with other beta-blockers. Initiate beta-blockers at a low-dose and up-titrate only after ECG assessment, if taking beta-blockers when starting dronedarone, an ECG should also be reviewed.

	Dronedarone could increase plasma concentrations of immunosuppressants (tacrolimus, sirolimus, everolimus and ciclosporin); plasma monitoring is recommended with co-administration. Combination of dronedarone with statins should be undertaken with caution, using lower starting and maintenance doses with monitoring for clinical signs of muscular toxicity. Potent CYP3A4 inducers such as rifampicin, phenobarbital, carbamazepine, phenytoin or St John's Wort are not recommended as they decrease dronedarone exposure. There is limited information on the optimal timing to switch from amiodarone to dronedarone. It should be borne in mind that amiodarone may have a long duration of action after discontinuation due to its long half-life. Monoamine oxidase inhibitors might reduce the clearance of the active metabolite of dronedarone; caution is recommended.
Reminder to ask patient about specific problems	Grapefruit juice beverages should be avoided when taking dronedarone

Section 6: Contra-indications, Cautions and Special Recommendations

Please list

CONTRAINDICATIONS:

1. Hypersensitivity to dronedarone or to any of the excipients: tablet core (hypromellose [E464], maize starch, crospovidone [E1202], poloxamer 407, lactose monohydrate, colloidal anhydrous silica, magnesium stearate [E572]); tablet coat (hypromellose [E464], macrogol 6000, titanium dioxide [E171] carnauba wax (E903])
2. Due to the presence of lactose in the formulation, patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take dronedarone tablets
3. Second-or-third-degree atrioventricular block, complete bundle branch block, distal block, sinus node dysfunction, atrial conduction defects, or sick sinus syndrome (except if used in conjunction with functioning pacemaker)
4. Bradycardia <50 beats per minute
5. Permanent AF with AF duration ≥ 6 months (or duration unknown), and attempts to restore sinus rhythm no longer considered by the physician
6. Patients in unstable haemodynamic conditions
7. History of or current heart failure, or left ventricular systolic dysfunction
8. Patients with liver or lung toxicity related to the previous use of amiodarone
9. Co-administration with potent cytochrome P450 3A4 inhibitors such as azole antifungals, macrolides, nefazodone and ritonavir
10. Medicinal products including torsades de pointes such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, terfenadine and certain oral macrolides, Class I and III antiarrhythmics
11. QTc interval ≥ 500 milliseconds
12. Severe hepatic impairment
13. Severe renal impairment (CrCl <30mL/min)
14. Co-administration with dabigatran

CAUTIONS:

1. Coronary artery disease
2. Corrent hypokalaemia and hypomagnesaemia before starting and during treatment

SPECIAL CONSIDERATIONS:

1. Manufacturer advises avoid in pregnancy – toxicity in animal studies
2. Manufacturer advises avoid in breast-feeding – present in milk in animal studies
3. The safety and efficacy of dronedarone in children aged below 18 years have not yet been established, no data are available
4. Efficacy and safety were comparable in elderly patients who did not suffer from other cardiovascular diseases, by comparison to younger patients

Section 7: Advice to the patient

Advice for prescribing clinician to inform patient

1. Take dronedarone tablets twice daily with morning and evening meals
2. To be compliant with attendance for blood test monitoring and appointments
3. Avoid consumption of grapefruit or grapefruit juice
4. Photoxicity may occur; patients should therefore take reasonable precautions to avoid excess exposure to sunlight, to apply broad-spectrum suncream blocking both UVA and UVB sunlight with a high sun-protective factor sunscreen during high sun exposure, and to wear protective clothing e.g. sunglasses, wide-brim hats and long-sleeve shirts.
5. Consult a healthcare professional immediately if experiencing symptoms of liver injury including fever, malaise, fatigue, yellowing of the skin or of the whites of the eyes, dark urine, itching
6. Consult a healthcare professional if experiencing symptoms of pulmonary toxicity including dyspnoea or non-productive cough
7. Consult a healthcare professional immediately if they develop any signs of heart failure such as weight gain, dependent oedema or increased dyspnoea
8. If a dose is missed, patients should take the next dose at the regular scheduled time and should not double the dose
9. If taking a concomitant statin, to monitor for signs of muscle toxicity and notify a healthcare professional immediately for symptoms including muscle pain, muscle weakness and tenderness

Section 8: Responsibilities for Secondary Care

Core responsibilities

1. Initiating treatment and prescribing for the first three months
2. Undertaking the clinical assessment and monitoring for the first month.
3. Communicate details of the above in 1 and 2 to GP within the first month of treatment. This information should be transferred in a timely manner.
4. Refer patients to GP and provide information of further action where appropriate e.g. blood test is due.
5. To provide advice to primary care when appropriate.
6. Review concurrent medications for potential interaction prior to initiation of dronedarone.
7. Stopping treatment where appropriate or providing advice on when to stop.
8. Reporting adverse events to the MHRA.
9. Reminder to ask patients about particular problems see section 5.

Other specific to drug

1. Click here to enter details

Section 9: Responsibilities for Primary Care

Core responsibilities

1.Responsible for taking over prescribing after the first three months

2. Responsible for the clinical assessment and monitoring after the first month 3. Review of any new concurrent medications for potential interactions. 4. Reporting adverse events to the MHRA. 5. Refer for advice to specialist where appropriate. 6. Reminder to ask patients about particular problems see section 5.
Other specific to drug
1. Click here to enter details

Section 10: Contact Details

Name	Organisation	Telephone Number	E mail address
Glen Cooper; Cardiac Pharmacist	UHB	0117 3422347	glen.cooper@uhbristol.nhs.uk
Daniel Griffiths; Cardiac Pharmacist	UHB	0117 3422347	daniel.griffiths@uhbristol.nhs.uk
Dr Palash Barman, Consultant Interventional Cardiologist	UHB	0117 3422013	palash.barman@uhbristol.nhs.uk
Dr Glyn Thomas, Consultant Interventional Cardiologist	UHB	Click here to enter details	glyn.thomas@uhbristol.nhs.uk
Rober Brown, Cardiology Pharmacist	NBT	0117 4142254	robert.brown@nbt.nhs.uk
Dr Paul Walker	NBT	0117 9505050	paul.walker@nbt.nhs.uk
Dr Mark Papouchado	NBT	0117 9505050	mark.papouchado@nbt.nhs.uk
Dr Phil Boreham	NBT	0117 9505050	philip.boreham@nbt.nhs.uk
Sarah Karthauser, Deputy Lead Pharmacist	WAHT	01934 647360	skarthauser@nhs.net

Section 11: Document Details

Date prepared	26/10/2010; reviewed May 2011, November 2011, March 2012, October 2018
Prepared by	Lloyds Mayers, Robert Brown @ NBT Daniela Ferro, Carolyn Shepherd @ UHB Revised by Jackie Criper November 2011 Revised by Nicola Bruce March 2012 Revised by Glen Cooper October 2018

Date approved by JFG	April 2018
Date of review	April 2020
Document Identification: Version	v2

Section 12: Collaboration

Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

1. Glen Cooper, Cardiac Pharmacist, University Hospitals Bristol NHS Foundation Trust
2. Robert Brown, Cardiology Pharmacist, North Bristol NHS Foundation Trust

Section 13: References

Please list references

1. Summary of Product Characteristics, 2014. Multaq 400mg tablets [online]. Accessed on 29/10/2018 via https://www.medicines.org.uk/emc/medicine/22894/SPC/Multaq+400mg+tablets/
2. British National Formulary, 2018. Dronedarone [online]. Accessed on 29/10/2018 via https://bnf.nice.org.uk/drug/dronedarone.html#indicationsAndDoses
3. NICE TA197, 2012. Dronedarone for the treatment of non-permanent atrial fibrillation [online]. Accessed on 29/10/2018 via https://www.nice.org.uk/guidance/ta197/chapter/1-Guidance
4. MHRA Drug Safety Update, 2014. Dronedarone (Multaq): cardiovascular, hepatic and pulmonary adverse events – new restrictions and monitoring requirements [online]. Accessed on 29/10/2018 via https://www.gov.uk/drug-safety-update/dronedarone-multaq-cardiovascular-hepatic-and-pulmonary-adverse-events-new-restrictions-and-monitoring-requirements