NHS Dudley The Dudley Group NHS Foundation Trust

EFFECTIVE SHARED CARE AGREEMENT

Dronedarone - For the treatment and management of atrial fibrillation

Specialist details Name	Patient identifier

INTRODUCTION

This shared care agreement outlines how the responsibilities for managing the prescribing of dronedarone for atrial fibrillation can be shared between the secondary care specialist and general practitioner (GP) / primary care prescriber. Dronedarone (Multaq®) is indicated in adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

The NICE final appraisal determination for dronedarone states: Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation **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** who have at least one of the following cardiovascular risk factors:
  - hypertension requiring drugs of at least two different classes
  - diabetes mellitus
  - previous transient ischaemic attack, stroke or systemic embolism
  - left atrial diameter of 50 mm or greater
  - left ventricular ejection fraction less than 40%, **or**
  - age 70 years or older, **and** who do not have unstable New York Heart Association (NYHA) class III or IV heart failure.

The recommended dose for dronedarone is 400 mg twice daily in adults. It should be taken as one tablet with the morning meal and one tablet with the evening meal. Guidance on the management of atrial fibrillation has been issued by NICE CG036 (2006) http://guidance.nice.org.uk/CG36 and Prodigy Clinical Knowledge Summaries http://cks.library.nhs.uk/atrial_fibrillation/view_whole_guidance. NICE has produced a final appraisal determination for dronedarone: Dronedarone for the treatment of non-permanent atrial fibrillation http://guidance.nice.org.uk/TA/Wave19/57/FAD/FinalAppraisalDetermination/pdf/English.

KEY PRINCIPLES FOR THE ESCA

Patient safety must be paramount.

The prescriber who prescribes dronedarone legally assumes clinical responsibility for the drug and the consequences of its use. Initiation doses of dronedarone should be prescribed by secondary care specialists; general practitioners should only prescribe maintenance doses.

RESPONSIBILITIES AND ROLES

Secondary care - specialist

Secondary care specialist to initiate dronedarone for the licensed indication in accordance with the manufacturer's Summary of Product Characteristics (SPC) and where treatment is proving effective, stabilise the patient on a maintenance dose consistent with the SPC.

Secondary care specialist to confirm absence of:

- Hypersensitivity to the active substance or to any of the excipients Second- or third-degree Atrio-Ventricular block or sick sinus rhythm (except when used in conjunction with a functioning pacemaker) Bradycardia <50 beats per minute Unstable haemodynamic conditions including patients with symptoms of heart failure at rest or with minimal exertion (corresponding with NYHA class IV and unstable class III patients) Co-administration with potent cytochrome P 450 (CYP) 3A4 inhibitors such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefadazone and ritonavir Co-administration with medicinal product inducing torsades de pointes such as phenothiazines, cisapride, bepridil, tricylcic antidepressants, terfenadine, oral macrolides, Class I and III antiarrhythmics QTc Bazett interval ≥500 milliseconds Potassium and magnesium deficiency

Secondary care specialist to ensure that patient's renal and hepatic function are monitored prior and during treatment initiation and ensure renal and hepatic function are not compromised as a result of treatment with dronedarone. Liver function tests should be performed prior to initiation of treatment with dronedarone and then repeated monthly for six months, at months 9 and 12, and periodically thereafter.

Secondary care specialist to discuss the benefits and possible common and uncommon side-effects of treatment with the patient including:

- advising the patient of the need to avoid ingesting grapefruit juice while taking dronedarone taking dronedarone with food that dronedarone interacts with a number of medicines and they should take advice prior to taking any new medicine including products such as St John's Wort for women of child bearing age that they must use reliable contraceptive methods whilst taking dronedarone

Secondary care specialist to assess potential adverse events and report these to the CSM.

Secondary care specialist to ensure that arrangements are in place for GPs to obtain advice and support where needed. Secondary care specialist to ensure that regular liver function tests of the patient (suggest monthly for the first 6 months and then 9 and 12 months post discharge then annually) are undertaken in primary care.

Primary care

Primary care physician to reply to the request from secondary care for shared care as soon as possible taking into account the extent of the care you are asked to be involved in e.g. prescribing of dronedarone, monitoring of treatment and/or patient's condition.

If in agreement, the primary care physician is to prescribe dronedarone at the dose at which the patient treatment has been stabilised after communication with the secondary care specialist.

Primary care physician to adjust dose of any concomitant medication known to interact with dronedarone as advised by the secondary care specialist.

Primary care physician to refer the patient back to the secondary care specialist if the patient's condition deteriorates. Particular attention should be paid to symptoms of heart failure - both in terms of patients developing heart failure and signs of deterioration in patients with existing heart failure.

It is the responsibility of the primary care physician to arrange for plasma creatinine levels to be monitored [at a time interval agreed with the secondary care specialist and patient]. Prior to assuming responsibility for managing patients with atrial fibrillation on dronedarone, the GP and secondary care specialist should agree the threshold for an increase in plasma creatinine that would prompt patient referral back to the secondary care specialist. A further change in creatinine levels is unlikely to be due to dronedarone but to some other condition and should prompt investigation for other causes of renal disease.

Primary care physician to ensure regular liver function tests of the patient (suggest monthly for the first 6 months and then 9 and 12 months post discharge then annually) are undertaken.

It is the responsibility of the primary care physician to arrange for an annual assessment of patient stability and symptomatic response using a 12 lead ECG (basic documented ECG rhythm, ECG intervals and conduction). Any significant, relative changes should prompt referral to the secondary care specialist for review. [Each local area will need to decide who has the requisite skills needed to interpret the ECG at this level and commission services accordingly.]

Due to the potential for significant drug-drug interactions, the primary care physician must ensure that the following are not taken with dronedarone:

- Ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, larithromycin, nefazodone, ritonavir, cisapride, bepridil, tricyclic antidepressants, terfenadine, flecainide, sotalol, amiodarone, propafenone, St. Johns Wort, grapefruit juice. (This list of interactions is not exhaustive. Please refer to the dronedarone SPC.)

Primary care physician to report adverse events to the specialist and CSM.

SUPPORTING INFORMATION

Licensed indication

Dronedarone (Multaq®) is indicated in adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

Dosage and administration

The recommended dose is 400 mg twice daily in adults. It should be taken as

- one tablet with the morning meal and one tablet with the evening meal.

Treatment with Class I or III antiarrhythmics (such as flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol, amiodarone) must be stopped before starting dronedarone.

Grapefruit juice should be avoided when taking dronedarone.

Elderly - Efficacy and safety were comparable in both elderly and younger patients. Although plasma exposure in elderly females was increased in a pharmacokinetic study conducted in healthy subjects, dose adjustments are not considered necessary.

Hepatic impairment - Dronedarone is contraindicated in patients with severe hepatic impairment because of the absence of data. No dose adjustment is required in patients with mild or moderate hepatic impairment.

Renal impairment - Dronedarone is contraindicated in patients with severe renal impairment (creatinine clearance [CrCl] <30 ml/min). No dose adjustment is required in other patients with renal impairment.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Patients in unstable hemodynamic conditions including patients with symptoms of heart failure at rest or with minimal exertion (corresponding with NYHA class IV and unstable class III patients).

QTc Bazett interval ≥500 milliseconds.

Medicinal products inducing torsades de pointes such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, terfenadine and certain oral macrolides, Class I and III antiarrhythmics are contraindicated because of the potential risk of proarrhythmia.

Caution should also be taken with co-administration with beta-blockers or digoxin.

Severe hepatic impairment.

Severe renal impairment (CrCl <30ml/min).

Co-administration with potent cytochrome P 450 (CYP) 3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir.

Patients with stable NYHA Class III heart failure or LVEF <35%.

Because of the unexplained results of the ANDROMEDA study, the use of dronedarone in unstable patients with NYHA class III and IV heart failure is contraindicated.

Because of limited experience in stable patients with recent (1 to 3 months) NYHA class III heart failure or with Left Ventricular Ejection Fraction (LVEF) <35%, the use of dronedarone is not recommended.

Bradycardia <50 beats per minute (bpm).

Second- or third-degree Atrio-Ventricular block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker).

Side-effects

The safety profile of dronedarone 400 mg twice daily in patients with atrial fibrillation (AF) or atrial flutter (AFL) is based on 5 placebo controlled studies, in which a total of 6,285 patients were randomised (3,282 patients received dronedarone 400 mg twice daily, and 2,875 received placebo). The mean exposure across studies was 13 months. In the ATHENA study, the maximum follow-up was 30 months.

Assessment of intrinsic factors such as gender or age on the incidence of any treatment emergent adverse reactions showed an interaction for gender (female patients) for the incidence of any adverse reactions and for serious adverse reactions.

In clinical trials, premature discontinuation due to adverse reactions occurred in 11.8% of the dronedarone-treated patients and in 7.7% in the placebo-treated group. The most common reasons for discontinuation of therapy with dronedarone were gastrointestinal disorders (3.2% of patients versus 1.8% in the placebo group). The most frequent adverse reactions observed with dronedarone 400 mg twice daily in the 5 studies were diarrhoea, nausea and vomiting, fatigue and asthenia.

Table 1 displays adverse reactions associated with dronedarone 400 mg twice daily in AF or AFL patients, presented by system organ class and by decreasing order of frequency.

System organ class	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1,000 to <1/100)	**Rare** (≥ 1/10,000 to <1/1,000)
Nervous system disorders			Dysgeusia	Ageusia
Cardiac disorders	Congestive heart failure	Bradycardia		
Gastrointestinal disorders		Diarrhoea Vomiting Nausea Abdominal pains		

		Dyspepsia		
Hepatobiliary disorders		Liver function test abnormalities		Hepatocellular liver injury, including life-threatening acute liver failure
Skin and subcutaneous tissue disorders		Rashes (including generalised, macular, maculo-papular) Pruritus	Erythemas (including erythema and rash erythematous) Eczema Photosensitivity reaction Dermatitis allergic Dermatitis	
General disorders and administration site conditions		Fatigue Asthenia		
Investigations	Blood creatinine increased QTc Bazett prolonged			

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000).

Monitoring

Patients with new or worsening heart failure during treatment

Use of dronedarone is contraindicated in patients with NYHA class IV and unstable class III heart failure (see section 4.3). There have been spontaneously reported events of new or worsening heart failure during treatment with dronedarone. Patients 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 or worsens, consider the suspension or discontinuation of dronedarone.

Liver Injury

Hepatocellular liver injury, including life ‑ threatening acute liver failure, has been reported in patients treated with dronedarone in the post ‑ marketing setting. Liver function tests should be performed prior to

initiation of treatment with dronedarone and then repeated monthly for six months, at months 9 and 12, and periodically thereafter. If ALT (alanine aminotransferase) 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. Appropriate investigation and close observation of patients should continue until normalisation of ALT. 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.

Electrolytes imbalance

Since antiarrhythmic medicinal products may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before initiation and during dronedarone therapy.

Management of plasma creatinine increase

It is recommended to measure plasma creatinine values 7 days after initiation of dronedarone. An increase in plasma creatinine has been observed with dronedarone 400mg twice daily in healthy subjects and in patients. This increase occurs early after treatment initiation and reaches a plateau after 7 days. If an increase in creatininemia is observed, this value should be used as the new reference baseline taking into account that this may be expected with dronedarone. An increase in creatininemia should not necessarily lead to the discontinuation of treatment with ACE-inhibitors or Angiotensin II Receptor Antagonists (AIIRAs).

QT prolongation

The pharmacological action of dronedarone may induce a moderate QTc Bazett prolongation (about 10 msec), related to prolonged repolarisation. These changes are linked to the therapeutic effect of dronedarone and do not reflect toxicity. Follow up, including ECG (electrocardiogram), is recommended during treatment. If QTc Bazett interval is ≥500 milliseconds, dronedarone should be stopped.

Interactions

Potent CYP3A4 inducers such as rifampicin, phenobarbital, carbamazepine, phenytoin or St John's Wort are not recommended. Administration of dronedarone to patients receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with digoxin toxicity. Clinical, ECG and biological monitoring is recommended, and digoxin dose should be halved. A synergistic effect on heart rate and atrioventricular conduction is also possible. The co-administration of beta-blockers or calcium antagonists with depressant effect on sinus and atrio-ventricular node should be undertaken with caution. These medicinal products should be initiated at low dose and up-titration should be done only after ECG assessment. In patients already on calcium antagonists or beta blockers at time of dronedarone initiation, an ECG should be performed and the dose should be adjusted if needed. 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. Patients should be warned to avoid grapefruit juice beverages while taking dronedarone.

BACK UP ADVICE AND SUPPORT

Secondary care contact details	Telephone No.	Fax	Email
Specialist - Cardiologist	01384-345111		Cardiologist e-mail
Hospital Pharmacy	01384-244031	01384-244007	Jane.Elvidge@nhs.net

Dudley Group NHS Foundation Trust

NHS Dudley

ESCA created using –

http://www.esca-keele.co.uk/dronedarone/agreement.php?ReferenceCode=989948FB

Original January 2011

Updated March 2016

Review date March 2019