LINCOLNSHIRE CLINICAL COMMISSIONING GROUPS in association with UNITED LINCOLNSHIRE HOSPITALS TRUST AND LINCOLNSHIRE PARTNERSHIP FOUNDATION TRUST

SHARED CARE GUIDELINE: Dronedarone for the treatment of patients with non-permanent atrial fibrillation.

General Principles

Shared Care Responsibilities:

In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. (*BNF* 70, September 2015 - March 2016, pg.4)

Aims:

(1) The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.

(2) Specific shared care guidance should be available for any high cost drug, high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.

(3) Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.

(4) Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies

Further copies of any guidelines in this series are available from members of the Arden and GEM commissioning Support Unit – Lincolnshire Prescribing & Medicines Optimisation Team.

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Principles of shared care

The General Medical Council published their Good Practice In Prescribing And Managing Medicines and which came into effect 25th February 2013. A section of the guidance provides recommendations for the sharing of care which applies to any instance when care is shared between different services.

Good practice recommendation 35.

- Decisions about who should take responsibility for continuing care or treatment after initial diagnosis or assessment should be based on patients best interest rather than on convenience or the cost of the medicine and associated monitoring or follow-up

Good practice recommendation 36.

- Shared care requires the agreement of all parties including the patient. Effective communication and continuing liaison between all parties to a shared care agreement is essential.

Good practice recommendation 37.

- If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence.

Good practice recommendation 38.

- If you delegate assessment of a patients' suitability for a medicine, you must be satisfied that the person to whom you delegate has the qualifications, experience, knowledge and skills to make the assessment. You must give them enough information about the patient to carry out the assessment required

Good practice recommendation 39.

- In both cases, you will be responsible for any prescription you sign.

Good practice recommendation 40.

- If you recommend that a colleague, for example a junior doctor or general practitioner, prescribes a particular medicine for a patient, you must consider their competence to do so. You must satisfy yourself that they have sufficient knowledge of the patient and the medicine, experience (especially in the case of junior doctors) and information to prescribe. You should be willing to answer their questions and otherwise assist them in caring for the patient, as required

Good practice recommendation 41

- If you share responsibility for a patient's care with a colleague , you must be competent to exercise your share of clinical responsibility.

You should:

a) Keep yourself informed about the medicines that are to be prescribed for the patient
b) Be able to recognise serious and frequently occurring adverse side effects
c) Make sure appropriate clinical monitoring arrangements are in place and that the patient and the healthcare professionals involved understand them
d) Keep up to date with relevance guidance on the use of the medicines and on the management of the patient's condition

Good practice recommendation 42

- In proposing a shared care arrangement, specialists may advise the patient's general practitioner which medicine to prescribe. If you are recommending a new or rarely prescribed medicine you should specify the dosage and means of administration and agree a protocol for treatment. You should explain the use of unlicensed medicines and departures from authoritative guidance or recommended treatments and provide both the general practitioner and the patient with sufficient information to permit the safe management of the patient's condition.

Good practice recommendation 43

- If you are uncertain about your competence to take responsibility for the patients continuing care you should seek further information or advice from the clinician with whom the patient's care is shared or from another experienced colleague. If you are still not satisfied you should explain this to the other clinician and to the patient and make appropriate arrangements for their continuing care.

Introduction

PACEF (2011) have approved Dronedarone as an AMBER drug subject for specialist initiation only. Subsequent continuation of therapy within primary care is supported by this shared care protocol.

GP's managing a patient with Atrial Fibrillation who feel their patient may benefit from Dronedarone therapy should seek specialist review under the terms of this shared care agreement.

NICE TA 197

In August 2010 the National Institute for Health and Clinical Excellence (NICE) published Technology Appraisal 197 (TA 197), which reviewed the use of dronedarone for the treatment of non-permanent atrial fibrillation. 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) (i.e. dronedarone is a second-line/third-line option), and
- **who have at least one of the following cardiovascular risk factors:** (1) hypertension requiring drugs of at least two different classes; (2) diabetes mellitus; (3) previous transient ischaemic attack, stroke or systemic embolism; (4) left atrial diameter of 50mm or greater; (5) left ventricular ejection fraction less than 40% (noting that the summary of product characteristics (SPC) does not recommend dronedarone for people with left ventricular ejection fraction less than 35% because of limited experience of using it in this group) or; (6) age 70 years or older and:
- **Who do not have unstable New York Heart Association (NYHA) class III or IV heart failure.**

American Food and Drug Administration (FDA) safety alert dronedarone

Recent reports from the American Food and Drug Administration (FDA) have highlighted cases of rare, but severe liver injury, including two cases of acute liver failure leading to transplant, in patients treated with dronedarone.

MHRA Drug Safety Update Vol 4 Issue 7 February 2011

The Medicines and Healthcare products Regulatory Agency (MHRA) has reported on both the risk of cardiac failure and hepatotoxicity with dronedarone. As well as concerns over severe liver injury already raised by the FDA, the MHRA also report a number of cases of new-onset heart failure associated with the drug. Advice to healthcare professionals is as follows:

- Patients should be advised to remain vigilant for the symptoms of heart failure (HF) or worsening of existing symptoms (e.g. weight gain, dependent oedema, increased dyspnoea). If HF develops or worsens, consider suspending or discontinuing dronedarone.
- For patients prescribed dronedarone, liver function tests (LFTs) should be performed: before treatment; on a monthly basis for 6 months; at months 9 and 12 and periodically thereafter. Existing patients on dronedarone should be contacted within the next month, so that LFTs can be initiated in line with the programme detailed above.
- Patients should be advised to remain vigilant for the symptoms of liver injury (e.g. abdominal pain or discomfort, loss of appetite, nausea, vomiting, yellowing of the skin or whites of the eyes, darkening of the urine, itching or fatigue).

Drug Details

Approved Name: **Dronedarone**
Brand Name: Multaq
Form and Strength: 400mg tablets

Specialist Responsibilities

The specialist secondary/tertiary care service will:

1. Discuss benefits and side effects of treatment with the patient/carer and obtain verbal informed consent that should be recorded in the medical notes.
2. Carry out base line liver function tests (LFTs) ,serum urea and electrolytes (U&Es), ECG and echocardiography. Consider pulmonary function tests.
3. Send a letter to the GP requesting that the GP participates in shared care. As part of the communication the GP should be signposted to where they can find a copy of the shared care protocol e.g. the PACEF website http://lincolnshire-pacef.nhs.uk/lincolnshire-prescribing-and-clinical-effectiveness-forum-pacef.
4. If GP agrees to shared care the specialist will initiate dronedarone in appropriate patients as specified by current national guidance (NICE TA 197). If GP declines invitation to shared care the specialist will still initiate dronedarone in appropriate patient's dependant on individual patient circumstances including ability to attend ULHT for regular monitoring and collection of medication. If patient unable to comply with this the specialist service may decide that dronedarone therapy is no longer appropriate.
5. Arrange a scheduled review to confirm efficacy of intervention.
6. Periodically review the patient's clinical condition and monitor response to treatment. Patients will not be discharged from specialist review unless they refuse or it becomes unreasonable i.e. frailty or terminal illness. In these circumstances the specialist will give advice to the GP in regards to the prospective management of these patients which may include discontinuation of therapy.
7. Provide the GP with details of outpatient consultations ideally within 14 days of seeing the patient or inform the GP if the patient does not attend the appointment.

8. Provide support to the GP and advice if treatment needs to be discontinued.
9. Review concomitant pharmaco-therapy and advise GP if switching or dose reduction should be considered i.e. Statins.

GP Responsibilities

The GP will:
1. Refer to specialist if patients with being managed by them are unresponsive to first line therapy and they require an opinion in regards to commencement of dronedarone therapy.
2. If contacted by the specialist in regards to shared care notify the consultant in writing, without undue delay, whether or not they agree to share care.
3. If accepting shared care prescribe dronedarone for the patient.
4. Monitor the patient's general overall health and wellbeing.
5. Carry out ongoing monitoring of liver function tests (LFT), urea and electrolytes (U&E) and 12 lead ECG noting the corrected QT interval time (QTC), heart rate and rhythm as detailed in monitoring section of this protocol.
6. Monitor the patient for adverse drug reactions and as this product has black triangle status report all adverse effects to the CSM through the Yellow Card system.
7. Refer back to the specialist if condition deteriorates as advised by specialist service.
8. Discontinue treatment (where necessary) on the advice of the specialist.

Referral Criteria

1. Patients will have received at least one month supply of dronedarone therapy on hospital prescription.
2. The specialist should arrange a scheduled review to confirm efficacy of treatment. Continue to prescribe Dronedarone until GP agrees to shared care.

Licensed Indications

Dronedarone is licensed for the maintenance of sinus rhythm after successful cardioversion adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF) Dronedarone should only be prescribed after alternative treatment options have been considered.

Recommended Dosage and Administration

The recommended dose is 400mg twice daily. It should be taken as one tablet with the morning meal and one tablet with the evening meal.
If a dose is missed the patient should be advised to take the next dose at the regular scheduled time and should not double the dose.

Background Pharmacology

Dronedarone is a multichannel blocker, affecting potassium, sodium and calcium channels in myocytes. This prolongs the cardiac action potential and refractory period, giving it a broad anti-arrhythmic effect.

Preparations Available

Dronedarone is available as 400mg tablets.

Adverse Effects

Common or very common side are: bradycardia (<50 beats per minute), gastro-intestinal disturbances (diarrhoea, nausea, vomiting and abdominal discomfort), QT prolongation, heart failure, malaise, rash, pruritus, raised serum creatinine.
Less common side effects taste disturbance, interstitial lung disease including pneumonitis and pulmonary fibrosis (investigate if symptoms such as dyspnoea or dry cough develop and discontinue treatment is confirmed), erythema, eczema, dermatitis, photosensitivity.
Rare – liver injury (including life threatening acute liver failure).
New onset or worsening heart failure reported; patients or their carers should be told how to recognise signs of heart failure and advised to seek prompt medical attention if symptoms such as weight gain, dependent oedema or dyspnoea develop or worsen. If heart failure or left ventricular systolic dysfunction develops, discontinue treatment.
Liver injury, including life threatening acute liver failure reported rarely. Liver function tests should be preformed prior to the initiation of treatment, monthly for first six months of treatment and periodically thereafter (see monitoring section page 5). Patients or their carers should be told to recognise signs of liver disorder and seek advice if symptoms such as abdominal pain, anorexia, nausea, vomiting, fever, malaise, itching, dark urine or jaundice develop.

(Information taken from British National Formulary (BNF) for further information refer to summary of product characteristics (SPC) for Multaq)

Drug Interactions

There are a number of drug interactions for dronedarone. The ones listed below as classed as Black dot – potentially serious interactions from the BNF.
Please refer to the BNF and the product SPC for further details.

Anti-arrhythmics

Increased myocardial depression. Avoid concomitant use with amiodarone or disopyramide as increased risk of ventricular arrhythmias.
Increased risk of myocardial depression when other anti-arrthymics given.

Antibacterials

Avoid concomitant use with clarithromycin, erythromycin,fidaxomicin, rifampicin and telithromycin

Anticoagulants

Possibly enhances anticoagulant effect of coumarins and phenidone.
Avoid concomitant use with dabigatran & rivaroxaban.

Antidepressants

Avoid concomitant use with citalopram and escitalopram due to risk of ventricular arrhythmias.
Avoid concomitant use with tricyclic antidepressants due to risk of ventricular arrhythmias.
Plasma concentration of dronedarone possibly reduced by St Johns wort, avoid concomitant use.

Antiepileptics

Avoid concomitant use with carmamazepine, fosphenytoin, phenobarbital, phenytoin and primidone as possibly reduce plasma concentration of dronedarone.

Antifungals

Avoid concomitant use with ketoconazole, itraconazole, posaconazole & voriconazole.

Antipsychotics

Increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval are given with antipsychotics that prolong the QT interval.
Manufacturer advises avoid concomitant use with phenothiazines as increased risk of ventricular arrhythmias.

Antivirals

Avoid concomitant use with ritonavir and saquinavir – risk of ventricular arrhythmias

Beta-blockers

Increased risk of myocardial depression when given with beta-blockers.
May increase plasma levels of metoprolol and propranolol.
Avoid use with sotalol as increased risk of ventricular arrhythmias.

Calcium channel blockers.

Plasma concentration of dronedarone increased by nifedipine,
Risk of bradycardia and myocardial depression when given with diltiazem and verapamil.

Cardiac Glycosides

Increases plasma concentration of digoxin, advise halve dose of digoxin.

Cytotoxics

Manufacturer advises avoid or reduce dose of bosutinab & ibrutinib as plasma concentration of both drugs increased by dronedarone.

Fingolimod

Increased risk of bradycardias.

Grapefruit juice

Increases plasma concentration of dronedarone avoid concomitant use.

Lipid regulating dugs

Increase plasma concentration of atorvastatin & rosuvastatin .
Increased risk of myopathy if given with simvastatin, manufacturer advises avoid concomitant use.

Lomitapide

Plasma concentration of lomitapide possibly increased.

Precautions and Contraindications

Contra-Indications:

Hypersensitivity to the active substance or any of the excipients
Liver or lung toxicity associated with previous amiodarone use
Second or third atrioventricular block, complete bundle branch block, distal block, sinus node dysfunction, atrial conduction defects or sick sinus syndrome (unless pacemaker fitted)
Bradycardia <50 beats per minute
Permanent AF with an AF duration ≥6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician
Patients with existing or previous heart failure or left ventricular systolic dysfunction.
Unstable hemodynamic conditions
Prolonged QT interval - QTc Bazett interval ≥500 milliseconds
Patients with liver and lung toxicity related to the previous use of amiodarone
Co-administration with potent cytochrome P 450 (CYP) 3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir
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
Severe hepatic impairment
Severe renal impairment avoid if eGFR less than 30ml/minute/1.73m^2

Due to the presence of lactose in preparation patients with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine.
Co-administration with dabigatran
Pregnancy: Manufacturer advises avoid, toxicity in animal studies.
Lactation: Manufacturer advises avoid as dronedarone present in milk in animal studies.

Precautions:

Coronary heart disease

Patients should be carefully evaluated for symptoms of Congestive Heart Failure. There have been spontaneously reported events of new or worsening heart failure during treatment with dronedarone. Patients should be advised to consult a clinician if they develop or experience signs or symptoms of heart failure, such as weight gain, dependent oedema, or increased dyspnoea (see adverse effects page 6). If heart failure develops, treatment with dronedarone should be discontinued.
Patients should be followed for the development of left ventricular systolic dysfunction during treatment. If left ventricular systolic dysfunction develops, treatment with dronedarone should be discontinued.
Caution is needed in patients with coronary artery disease

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.(see contraindications page 7).
Based on clinical experience, dronedarone has a low pro-arrhythmic effect, however pro- arrhythmic effects may occur in particular situations with concomitant use of medicinal products favouring arrhythmia and/or electrolyte disorders.

Electrolyte in balance

Correct hypokalaemia and hypomagnesaemia before starting and during treatment.

Liver injury

Hepatocellular liver injury, including life-threatening acute liver failure, has been reported in patients treated with MULTAQ in the post-marketing setting. Liver function tests should be performed prior to initiation of treatment with dronedarone and during tretament (see monitoring sections) Patients should be advised to report Any symptoms of potential liver injury (see adverse effects page 6)

Management of plasma creatinine increase

An increase in plasma creatinine (mean increase 10 µmol/L) has been observed with dronedarone 400 mg twice daily in healthy subjects and in patients. In most patients this increase occurs early after treatment initiation and reaches a plateau after 7 days. It is recommended to measure plasma creatinine values prior to and 7 days after initiation of dronedarone (see monitoring section page 9). If an increase in creatininemia is observed, serum creatinine should be re-measured after a further 7 days. If no further increase in creatinaemia is observed, this value should be used as the new reference baseline taking into account that this may be expected with dronedarone. If serum creatinine continues to rise then consideration should be given to further investigation and discontinuing treatment.

Respiratory and lung disorders

Cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported in post-marketing experience. Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity and patients should be carefully evaluated clinically. If pulmonary toxicity is confirmed treatment should be discontinued. (see adverse effects page 6)

Use in the elderly
Caution is needed in elderly patients ≥75 years with multiple co-morbidities
Use in Children
Safety and effectiveness in children have not been established.

Monitoring

Baseline:
ECG, echocardiogram, Liver function tests (LFTs), serum electrolytes and urea.

Thereafter – LFTs 1 week after initiation of treatment, then at 1 month and then monthly for first 6 months of treatment; at months 9 and 12 and periodically thereafter as instructed by the specialist team with a minimum regime of 6 monthly sampling.

Thereafter – U&Es and plasma creatinine , 1 week after initiation of treatment, repeat after 7 days if see an increase in plasma creatinine. If no increase after 7 days take this value as new reference baseline. If continue to see increase seek specialist advice, and more frequent monitoring may be required.
Continue to monitor at 6 months of treatment, 12 months of treatment and periodically thereafter as instructed by the specialist team with a minimum regime of 6 monthly sampling.

Thereafter – ECGs at 6 months of treatment, 12 months of treatment and periodically as instructed by the specialist team with a minimum regime of 12 monthly sampling. Clinicians are advised to monitor heart rate, rhythm and QTC interval (should be less than 500milliseconds). If it is not possible to facilitate this in primary care, then this should be identified in replying to the shared care agreement so that it can be arranged by the specialist team locally.

Patients should be advised to report any potential signs of liver injury such as new onset abdominal pain or discomfort, loss of appetite or anorexia, nausea, vomiting, fatigue, jaundice (yellowing of the skin or whites of the eyes), dark urine or itching to their GP.
Patients should be advised to remain vigilant for the symptoms of heart failure or worsening of existing symptoms e.g. weight gain, dependant oedema, and increased dyspnoea.
Patients should be advised to report any possible signs of pulmonary toxicity such as onset of dyspnoea or non-productive cough. If pulmonary toxicity suspected treatment should be discontinued and urgent advice sought from the specialist.
If monitoring parameters fall outside of normal or individually prior agreed ranges then specialist advice should be sort.

The MHRA advise that treatment should be stopped and advice from specialist sort if:
- **LFTS outside normal values**
- **Patient develops symptoms suggestive of liver injury**
- **Patients develop symptoms suggestive of heart failure or existing heart failure worsens**

Indication of Likely Cost of Therapy in Primary Care

MIMS February 2016
Dronedarone 400mg twice daily £63.00 for 28 days treatment

Information Given to the Patient

Specialist should discuss risks versus benefit of dronedarone therapy with patient and record verbal consent in the medical notes prior to initiation.

Contact Details

Grantham Hospital Cardiology Team
Cardiology Secretaries (01476) 464791

Lincoln County Hospital Cardiology Team
Cardiology Secretaries (0152) 573800

Pilgrim Hospital Cardiology Team
Cardiology Secretaries (01205) 445538

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