LINCOLNSHIRE CLINICAL COMMISSIONING GROUPS in association with UNITED LINCOLNSHIRE HOSPITALS 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 74, September 2017 – March 2018, pg.5)

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 Optum Medicines Management and Optimisation Team.

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Principles of shared care

NHS England published Guidance - Responsibility for Prescribing between primary, secondary and tertiary care – January 2018.
Key recommendations from guidance:

1.0 Introduction

1.1 Shared Care Prescribing guidelines are local policies to enable General Practitioners to accept responsibility for the prescribing and monitoring of medicines/ treatments in primary care in agreement with the initiating service.
1.4 Where possible shared acre should be disease specific rather than medicine specific and link into complement local integrated care pathways and shared acre policies. Medicines and conditions suitable for shared care will be identified by local medicines committees and will be classified as AMBER (AMBER 1 for Lincolnshire) through the traffic light system. … However it should be remembered that the provision of shared care prescribing guidelines does not necessarily mean that the GP has to agree to accept clinical and legal responsibility for prescribing; that they should only do so if they feel clinically confident in managing that condition.

2.3 reasonable predictable clinical situation

2.3.1 Transfer of clinical responsibility to primary care should only be considered where the person's clinical condition is stale or predictable.

2.4 Agreement of shared care between consultant and GP

2.4.1 Referral to the GP should only take place once the GP has agreed in each individual case and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities. The GP should confirm the agreement and acceptance of the shared care prescribing arrangement and that the supply arrangements have been finalised. The secondary/ tertiary provider must supply an adequate amount of the medication to cover the transition period. The patiet should then be informed to obtain further prescriptions from the GP.

2.7 Clear definition of responsibility

2.7.1 The areas of care for which each clinician has responsibility should be clearly defined.

2.8 Clinical responsibility

2.8.1 Clinical responsibility for prescribing is held by the person signing the prescription who must also ensure adequate monitoring.

2.9 Communication network & emergency support

2.9.1.Telephone details and (if appropriate) secure email addresses of both parties should be exchanged and recorded. This will enable the practice to access timely advice, guidance and information if problems arise, and will also enable secondary care clinicians to easily contact the GP if necessary. This should include out of hours contact numbers, how to access the on-call duty doctor. Patients and their carers should also be provided with contact details for support and help if required both in and out of hours.
2.9.2 People who are being treated on the advice of a secondary acre team, but are no longer being seen in that setting , may still need a review should problems arise. The appropriate level of care or advice should be available from the secondary care team in a timely manner without necessarily requiring a new referral.

6.0 Monitoring

6.0.1 All appropriate monitoring arrangements must be fulfilled. The person delivering that aspect of the shared care agreement should ensure that the resources to do this are in place in the clinical setting in which they are delivered.

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 in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF) when alternative treatments are unsuitable . Treatment should be initiated under specialist supervision.

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

For further information on adverse effects please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk

Common or very common adverse effects

Asthenia, bradycardia (<50 beats per minute),congestive heart failure, gastro-intestinal disturbances (diarrhoea, nausea, vomiting and abdominal discomfort), QT prolongation, skin reactions.

Uncommon adverse effects

Photosensitivity reactions, respiratory disorders, taste disturbance.

Rare or very rare

Hepatic disorders, vasculitis.

Adverse effects further information

Heart 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

Liver injury, including life threatening acute liver failure reported rarely.discontinue treatment if 2 consecutive alanine aminotransferase concentrations exceed 3 times upper limit of normal. Liver function tests should be performed 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.

Pulmonary toxicity

Interstitial lung disease, pneumonitis and pulmonary fibrosis reported. Investigate if symptoms such as dyspnoea or dry cough develop and discontinue if confirmed.

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

Drug Interactions

For detailed information on drug interactions, please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk
Below is a summary of some of the key interactions.

Drugs that increase risk of torsade de pointes.

Co-prescribing of medicinal products that induce torsades de pointes such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, certain oral macrolides (such as erythromycin) , terfenadine and Class I and III antiarrthymics are contraindicated because of potential risk of proarrhythmia. Caution should also be taken with co-administration with beta-blockers or digoxin.

Potent CYP 3A4 inhibitors

Doses of 200mg ketoconazole daily result in 17 fold increase in dronedarone exposure. Avoid concomitant use with ketoconazole and other potent CYP 3A4 inhibitors such as fluconazole, itraconazole, posaconazole, voriconazole, ritonavir,telithromycin, clarithromycin and nefazodone.

CYP 3A4 inducers

Rifampicin (600mg once daily) decreased dronedarone exposure by 80%. Co-administration of rifampicin and other potent CYP 3A4 inducers such as phenobarbital, carbamazepine, phenytoin or St John's Wort is not recommended.

Anticoagulants

Possibly enhances anticoagulant effect of coumarins and phenidone.
Avoid concomitant use with dabigatran & rivaroxaban.
Possibly increases exposure to apixaban.
Dronedarone slightly increases exposure to edoxaban,. Manufacturer advises adjust dose.

Antiepileptics

Avoid concomitant use with carmamazepine, fosphenytoin, phenobarbital, phenytoin and primidone as possibly reduce plasma concentration of dronedarone.
Avoid concomitant use with ritonavir and saquinavir – risk of ventricular arrhythmias

Beta-blockers

Increase risk of cardiovascular side effects. Manufacturer advises use with caution or avoid.

Calcium channel blockers.

Amolodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, verapamil, - dronedarone predicted to increase exposure to these drugs.

Plasma concentration of dronedarone increased by diltiazem

Risk of bradycardia and myocardial depression when given with diltiazem and verapamil.

Cardiac Glycosides

Increases plasma concentration of digoxin,manufacturer advises monitor and adjust dose of digoxin.

Grapefruit juice

Increases plasma concentration of dronedarone avoid concomitant use.

Lipid regulating dugs

Increase plasma concentration of atorvastatin & rosuvastatin . Manufacture advises monitor and adjust dose.

Increased risk of myopathy if given with simvastatin, manufacturer advises avoid concomitant use.

Precautions and Contraindications

For further information on contraindications and cautions in use, please refer to the online BNF which can be accessed via

https://bnf.nice.org.uk/

or from the Summary of Product Characteristics which can be accessed via:

www.medicines.org.uk

Contra-Indications:

Hypersensitivity to the active substance or any of the excipients.

Liver toxicity associated with previous amiodarone use.

Lung toxicity associated with previous amiodarone use.

Atrial conduction defects, 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.

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

Drug tariff November 2018
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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