United Lincolnshire Hospitals NHS
NHS Trust

NHS Lincolnshire

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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* 61, March 2011, 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 PCT Prescribing Advisers.

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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) and echocardiography.
3. Send a letter to the GP providing the details of diagnosis, relevant clinical information and baseline results suggesting that shared care is agreed for this patient and send a link to or a copy of the shared care protocol.
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 treatment of 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.

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

Very common side effects are changes in blood creatinine levels and changes in ECG. Common side effects include bradycardia (<50 beats per minute), diarrhoea, nausea, vomiting and abdominal discomfort. Itching may occur and rarely inflammatory skin disease may either manifest or worsen in known suffers.
Less common side effects include a change in sense of taste.
Hepatocellular liver injury including life threatening acute liver failure has been reported in patients treated with dronedarone. 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)

Drug Interactions

Dronedarone is contraindicated with QT prolonging drugs e.g. phenothiazines, tricyclic antidepressants and potent cytochrome P450 3A4 inhibitors.
Statins should be used with caution. Consider switching statin to a statin with lower P450 profile for example rosuvastatin or pravastatin. Lower starting dose and maintenance dose should be used and patients should be monitored for muscular toxicity.
Co- prescribing of cytochrome P34A inducers such as rifampicin, phenobarbital, carbamazepine or St John's Wort is not recommended.

Precautions and Contraindications

Contra-Indications:

Hypersensitivity to the active substance or any of the excipients
Second or third atrioventricular block or sick sinus syndrome (except when used in conjunction with a pacemaker)
Bradycardia <50 beats per minute
Patients with unstable hemodynamic conditions including patients with symptoms of heart failure classified as NYHA class lV and unstable class lll.
QTc Bazett interval ≥500 milliseconds
Severe hepatic impairment
Severe renal impairment (CrCL <30ml/min)
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.

Precautions:

Electrolyte in-balance – Since anti-arrhythmic drugs may be ineffective in patients with either hypokalemia ,any potassium or magnesium deficiency this should be corrected before initiation and during dronedarone therapy.

Pregnancy: Use of dronedarone is not recommended in pregnancy due to lack of data.
Lactation: it is not known whether dronedarone is excreted in human breast milk.
Children: Safety and effectiveness in children have not been established.

Monitoring

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

Thereafter – LFTs 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 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. Clinicians are advised to monitor heart rate, rhythm and

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, increased dyspnoea.

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

Dronedarone 400mg twice daily £63.00 for 28 days treatment (May 2011).

Information Given to the Patient

Specialist should discuss risks vrs 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

References

1. NICE Technology Appraisal 197:Dronedarone for the treatment of non-permanent Atrial Fibrillation August 2010.
2. MHRA Drug Safety Update Vol 4 Issue 7 February 2011
3. North of Tyne Area Prescribing Committee Shared care Group. Dronedarone-Information for primary care. July 2010.
4. Summary Product Characteristics (SPC) Multaq 400mg tablets Sanofi Aventis. Last updated 9th February 2011, eMC website.

Authors

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