November 2011

Dronedarone ▼ (Multaq®)
For the treatment and management of non permanent atrial fibrillation

INTRODUCTION

There should be willing consent of all parties to enter into a shared care agreement. This includes patients (plus carers if necessary) and prescribers (i.e. general practitioners / primary care prescribers and consultants / secondary care prescribers). If a general practitioner is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility (including prescribing) for the patient remains with the secondary care specialist.

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.

Dronedarone is not licensed for permanent AF i.e. AF that fails to terminate using cardioversion, or is terminated but relapses within 24 hours, or long-lasting persistent AF (usually longer than 1 year) in which cardioversion has not been indicated or attempted

The NICE TA 197 for dronedarone was issued in July 2010 and a subsequent review by the EMA in September 2011 (Appendix) such that the Summary of Product Characteristics has been changed:

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

Dronedarone should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.

Based on this and the previous NICE guidance Dronedarone is now recommended as an option for the treatment of non-permanent atrial fibrillation **only** in people as outlined above, after

confirmation using the checklist in the appendix , and:

- 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
  - age 70 years or older

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.

KEY PRINCIPLES FOR THE SHARED CARE PROTOCOL

Prescribing responsibility should only be considered for transfer to primary care when a patient's clinical management and treatment is demonstrably stable.

Initiation doses of dronedarone should be prescribed by Consultant Cardiologist ONLY; general practitioners should only prescribe maintenance doses.

The prescriber who prescribes dronedarone legally assumes clinical responsibility for the drug and the consequences of its use.

RESPONSIBILITIES AND ROLES

Secondary care – Consultant Cardiologist

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 syndrome (except when used in conjunction with a functioning pacemaker)
- Bradycardia <50 beats per minute
- Unstable haemodynamic conditions including patients with any symptoms/signs of heart failure
- Co-administration with potent cytochrome P 450 (CYP) 3A4 inhibitors such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin,

nefazodone 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 ≥500 milliseconds

- Potassium and magnesium deficiency

To establish a baseline of the patient's renal and hepatic function prior to initiation of dronedarone to confirm absence of severe renal and hepatic failure.

To discuss the benefits and possible common and uncommon side-effects of treatment with the patient including:

- advising to 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.
- 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

To initiate and prescribe dronedarone (as appropriate) and where treatment is proving effective, stabilise the patient on a maintenance dose.

To ensure that patient's renal and hepatic function are monitored during treatment initiation (7 to 10 days post initiation) and ensure renal and hepatic function are not compromised as a result of treatment with dronedarone.

Prescribing responsibility should only be considered for transfer to primary care when a patient's clinical management and treatment is demonstrably stable. Due to increases in plasma creatinine observed with dronedarone 400mg, a patient's baseline creatinine should be stable prior to transfer to primary care. Dronedarone is expected to increase serum creatinine by approximately 10 micromol/l at the time of initiation. This does not reflect changes in underlying renal function and should not necessarily trigger the discontinuation of other drugs, especially ACE inhibitors or Angiotensin II Receptor Antagonists (AIIRAs).

Consultant Cardiologist to assess potential adverse events and report these to the CSM.

Consultant Cardiologist to communicate promptly with the GP when treatment is changed and to advise on any implications of co-prescribing with current medications; particular caution with:-

- Potent CYP3A4 inducers such as rifampicin, phenobarbitone, carbamazepine, phenytoin or St John's Wort Digoxin, beta-blockers, calcium antagonists, statins, sirolimus, tacrolimus, angiotensin-converting enzyme inhibitors including dose adjustment of dronedarone or any of the above drugs

Consultant team to undertake regular follow up of the patient with particular emphasis on identifying transition to permanent AF when dronedarone should be discontinued (suggest 3,6, 9 and 12 months post initiation of therapy, and then every 6 months at least).

Consultant team to arrange for plasma creatinine levels (eGFR) to be monitored annually (may be done in association with GP).

Consultant team to arrange for a 6 monthly assessment of patient stability and symptomatic response using a 12 lead ECG (basic documented ECG rhythm, ECG intervals and conduction).

Primary care

GP to prescribe dronedarone at the dose at which the patient treatment has been stabilised after communication with the secondary care specialist.

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

GP to refer the patient back to the secondary care specialist if the patient's condition deteriorates between reviews. 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 heart failure.

In line with the Appendix (Sanofi Information on severe liver injury associated with the use of Multaq (dronedarone) January 2011) Liver Function Tests should be performed on a monthly basis for 6 months, at 9 and 12 months and periodically thereafter, and should be performed in conjunction with the Consultant team.

GP to report adverse events to the specialist and CSM.

Due to the potential for significant drug-drug interactions, the GP 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.)

Patient's role (or that of carer)

Report to the specialist or GP if he/she does not have a clear understanding of the treatment.

Share any concerns in relation to treatment with dronedarone. Pay particular attention to any other medicines being taken whilst receiving dronedarone.

Patients should be advised to 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.

He/she must not take St John's Wort or drink grapefruit juice whilst receiving dronedarone.

Present rapidly to the GP or secondary care specialist should their condition significantly worsen.

If he/she develops symptoms suggestive of heart failure, the patient must immediately notify the GP or secondary care specialist i.e. if he/she develops any of the following:

- Increasing swelling of the feet or legs
- Wheezing, chest tightness or coughing up frothy sputum at rest, night time or after minor exertion
- Using more pillows to prop themself up at night so they can breathe more easily
- Gaining more than 5 pounds or 2-3 kilograms in weight in a short period of time

Notify the GP or secondary care specialist if physical activity causes shortness of breath or if he/she has shortness of breath while at rest or after a small amount of exercise.

Immediately notify the GP or secondary care specialist if they have severe heart failure or have been hospitalised for heart failure within the last month.

The patient must not take dronedarone if they have heart failure.

Report any adverse effects to the specialist or GP whilst taking dronedarone.

BACK UP ADVICE AND SUPPORT

Secondary care contact details	Telephone No.	Bleep	Fax	Email
Specialist	Dr K Rajappan 01865 221514	4535	01865 740409	kim.rajappan@ouh.nhs.uk
Hospital Pharmacy	-	-	-	-
Other	-	-	-	-

Appendix 1

19 January 2011

Information on severe liver injury associated with the use of Multaq (dronedarone).

Dear Healthcare Professional

- **Summary**
  - Cases of liver injury, including two cases of liver failure requiring transplantation have been reported in patients receiving dronedarone. Some of these cases have occurred early after start of treatment.
  - For patients prescribed dronedarone, liver function tests should be performed:
    - prior to treatment,
    - on a monthly basis for six months,
    - at months 9 and 12, and periodically thereafter.
  - Patients currently receiving dronedarone should be contacted within the next month so that liver function tests could be performed and thereafter they should be tested as listed above depending on when treatment was initiated
  - If alanine transaminase (ALT) levels are elevated to ≥3 × upper limit of normal (ULN), levels should be re-measured within 48 to 72 hours. If ALT levels are confirmed to be ≥3 × ULN after re-measurement, dronedarone treatment should be withdrawn.
  - Patients should be advised to contact health care professionals immediately in case of signs or symptoms of liver injury.

The communication of this information has been agreed with the European Medicines Agency (EMA) and National Competent Authorities.

- **Further information on the safety concern**

Dronedarone 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.

Since dronedarone was licensed in 2009, there have been reports of liver function test abnormalities and hepatocellular liver injury in patients taking dronedarone, including two case reports of acute liver failure requiring transplantation. The two case reports of liver transplantation occurred at 4.5 and 6 months after initiation of treatment in patients with normal baseline liver function tests. In one case the liver injury was not reversible after discontinuation of dronedarone. Although both patients were taking concomitant medications, a causal relationship with dronedarone could not be excluded.

- The Section 4.4 “Warnings and Precautions for use” of the Summary of Product Characteristics (SmPC) will be updated with these new specific recommendations:

- 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 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 normalization of ALT.
- Patients should be advised to 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.

- The Section 4.8 "Undesirable effect" of the SmPC will include hepatic adverse drug reactions (i.e., liver function test abnormal (frequency common ≥1/100 to <1/10) and hepatocellular liver injury, including life-threatening acute liver failure (frequency rare ≥1/10,000 to <1/1,000).

For patients currently taking dronedarone liver function tests should be performed within the next month and thereafter according to the recommendations in the prescribing information taking into account when treatment with dronedarone was started. Prescribers are reminded that dronedarone is contraindicated in patients with severe hepatic impairment.

- **Call for reporting:**

Healthcare professionals should report any serious adverse events suspected to be associated with the use of Multaq to the Medicines and Healthcare products Regulatory Agency using a Yellow Card available directly from the MHRA, CHM Freepost, London SW8 5BR, or electronically via the MHRA website (www.yellowcard.gov.uk). In addition, this information may be reported to the Sanofi-aventis UK Pharmacovigilance department at:

Sanofi-aventis, One Onslow Street, Guildford, Surrey, GU1 4YS, UK
Tel: 01483 554242
Fax: 01483 554806
Email: uk-drugsafety@sanofi-aventis.com.

Communication information

The product information (SmPC and patient information leaflet) will be revised to include this information and will be distributed once it has been reviewed and approved by the EMA.

Updated educational materials will be distributed when available.

If you have any questions or require additional information, please call Medical Information Services at Sanofi-aventis, One Onslow Street, Guildford, Surrey, GU1 4YS, UK
Tel: 01483 554919
Fax: 01483 535432
Email: uk-medicalinformation@sanofi-aventis.com.

Yours sincerely,

Dr Tony Whitehead
Medical Director
Sanofi-aventis

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 September 2011
EMA/CHMP/706259/2011
EMEA/H/C/1043/A20/005

What are the conclusions of the CHMP?

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that there was a risk of Multaq causing injury to the liver as well as the lung. The Committee also concluded that, although the population in the PALLAS trial (permanent atrial fibrillation with several risk factors) differs from the currently approved population (non-permanent atrial fibrillation), the cardiovascular findings from the study were significant and could be relevant for the currently approved population.

In order to ensure that the benefits of Multaq continue to outweigh its risks, the CHMP considered that restrictions and other measures were needed to minimize the risk of adverse liver, lung and cardiovascular events. The Committee is issuing a number of risk minimisation measures which include recommendations in the prescribing information on the use of Multaq.

The Committee has agreed with the company on a letter to be sent out shortly to prescribers in the EU explaining the changes to the prescribing information as well as educational material for prescribers.

The amended information to doctors and patients can be found here.

What are the recommendations for patients and prescribers?

- Multaq should only be prescribed if other antiarrhythmic medicines have been considered.
- Multaq should only be used for maintaining heart rhythm in patients with persistent and paroxysmal atrial fibrillation (types of non-permanent atrial fibrillation) and whose normal heart rhythm has been restored.
- Treatment with Multaq should only be started and monitored by a specialist.
- Prescribers should consider discontinuing Multaq if atrial fibrillation reoccurs.
- Switching treatment from amiodarone to Multaq should be done cautiously by a specialist.
- Multaq must not be given to patients with permanent atrial fibrillation.

- Multaq must not be given to patients with left ventricular systolic dysfunction (impairment affecting the left side of the heart) or patients who have had or have heart failure.
- Patients who have had previous liver or lung injury following treatment with amiodarone, another antiarrhythmic medicine, must not be given Multaq.
- Patients on Multaq should have their lung and liver function as well as their heart rhythm regularly monitored. Especially liver function should be monitored more closely during the first few weeks. Kidney function should also be monitored during the first week of treatment.
- Patients currently on Multaq are recommended to have their treatment evaluated by their doctor at their next scheduled appointment.
- Patients who have any questions should speak to their doctor or pharmacist.

A European Commission decision on this opinion will be issued in due course.

The current European public assessment report for Multaq can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.

MULTAQ® (Dronedarone) Prescriber Checklist

[Version dated 20 September 2011]

This checklist can assist you when prescribing MULTAQ®. Treatment with MULTAQ® should be initiated and monitored only under specialist supervision. Treatment with MULTAQ® can be initiated in an outpatient setting. See the SPC for full prescribing information.

MULTAQ® 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 (see sections 4.3 and 4.4), MULTAQ® should only be prescribed after alternative treatment options have been considered. MULTAQ® should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.

There is limited information on the optimal timing to switch from amiodarone to MULTAQ®. Amiodarone may have a long duration of action after discontinuation due to its long half life.

If any of the criteria below is checked **YES**, do not prescribe MULTAQ®.

Medical Conditions	YES	NO
- The patient has hypersensitivity to the active substance or to any of the excipients.	☐	☐
- The patient has 2nd or 3rd degree atrio-ventricular block, complete bundle branch block, distal block, sinus node dysfunction, atrial conduction defects, or sick sinus syndrome (except when used in conjunction with a functioning pacemaker).	☐	☐
- The patient has bradycardia (<50 beats per minute).	☐	☐
- The patient has permanent AF with an AF duration ≥ 6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician.	☐	☐
- The patient has a history of, or current heart failure or left ventricular systolic dysfunction.	☐	☐
- The patient has severe hepatic impairment.	☐	☐
- The patient has severe renal impairment (CrCl <30ml/min).	☐	☐
- The patient has experienced liver or lung toxicity related to the previous use of amiodarone.	☐	☐
- The patient has a QTc Bazett interval ≥500 milliseconds.	☐	☐
Concomitant Medications		
- The patient is currently being treated with potent cytochrome P450 (CYP) 3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir)	☐	☐
- The patient is using medicinal products inducing torsades de pointes (e.g. phenothiazines, cisapride, bepridil, tricyclic antidepressants, terfenadine and certain oral macrolides [such as erythromycin], Class I and III antiarrhythmics)	☐	☐

The following main assessments are recommended before starting and during MULTAQ® therapy.

Assessments at initiation of MULTAQ

☐ ECG	☐ Digoxin, beta blockers, calcium antagonists, statins
☐ LVEF, CHF status	☐ Anticoagulation if needed as per clinical AF guidelines
☐ Liver function tests	☐ Concomitant medications
☐ Serum creatinine level	

Planned assessments for the 6 months following initiation of treatment

- ☐ Serial ECGs, at least every 6 months
- ☐ Liver function tests:
  - ☐ Day 7
  - ☐ Month 1 ☐ Month 2 ☐ Month 3
  - ☐ Month 4 ☐ Month 5 ☐ Month 6
- ☐ Serum creatinine level at Day 7

Planned assessments from Month 6 to Year 1

- ☐ ECG at Month 12
- ☐ Liver function tests at Month 9
- ☐ Liver function tests at Month 12

Planned assessments beyond Year 1

- ☐ Serial ECGs, at least every 6 months
- ☐ Periodic liver function tests