

PRESCRIBING STATUS OF DRONEDARONE (MULTAQ[®]▼)

1.0 PURPOSE

The purpose of this paper is to address outstanding issues relating to the prescribing of dronedarone (Multaq[®]▼) raised by professionals and highlighted to the All Wales Prescribing Advisory Group (AWPAG). This paper is pertinent to recommendation 46 of the AWMSG Medicines Strategy for Wales paper¹:

“AWMSG will examine the applicability of shared care arrangements to specialist areas of prescribing and where appropriate, develop shared care templates.”

2.0 BACKGROUND

Dronedarone is now indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF)². Due to its safety profile dronedarone should only be prescribed after alternative treatment options have been considered.

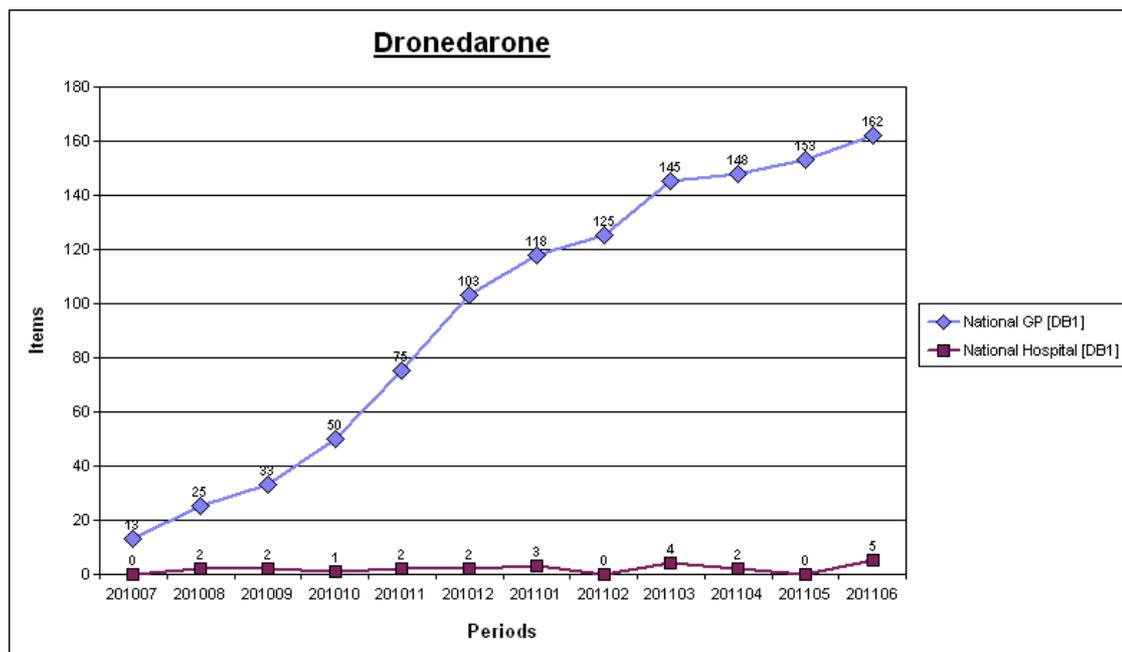
All Wales prescribing data shows an increasing trend over the past year, particularly in general practice, for the number of items prescribed (see Figure 1). Therefore, in July 2011, AWPAG considered dronedarone against the AWMSG shared care criteria (see Appendix 1).

The Good Practice in Prescribing Medicines guidance, issued by the General Medical Council, provides two statements regarding the responsibility for prescribing medicines for hospital outpatients³:

- If you are the doctor signing and issuing the prescription you bear responsibility for that treatment; it is therefore important that, as the prescriber, you understand the patient's condition as well as the treatment prescribed and can recognise any adverse side effects of the medicine should they occur.
- There should be full consultation and agreement between general practitioners and hospital doctors about the indications and need for particular therapies. The decision about who should take responsibility for continuing care or treatment after initial diagnosis or assessment should be based on the patient's best interests rather than on the healthcare professional's convenience or the cost of the medicine.

AWPAG initially proposed that the prescription of dronedarone be hospital-only for a minimum of six months and suitable for shared care prescribing thereafter. National consultation was, however, postponed pending the outcome of a European Medicines Agency (EMA) review in September 2011.

Figure 1. All Wales prescribing data for dronedarone.



2.1. The EMA statement

The Committee for Medicinal Products for Human Use (CHMP) considered that the availability of a range of treatments for a difficult condition such as AF was important and that for some patients with non-permanent AF dronedarone remains a useful treatment option⁴. CHMP was therefore of the opinion that the benefits of dronedarone outweigh its risks in these patients, provided that further changes to the information for prescribers and patients are introduced to minimise the risk of injury to the liver, lung and heart. For further details of the risk minimisation strategies refer to the full EMA statement (see Appendix 2).

To support safer use, drug safety advice from MHRA states that:

“Patients should have their treatment reviewed at the next routine appointment to ensure that they remain eligible for dronedarone treatment according to the revised prescribing information, including new restrictions on use.”⁵

3.0 RECOMMENDATION

At their meeting on 9 November 2011, the All Wales Medicines Strategy Group (AWMSG) endorsed the recommendation that dronedarone (Multaq[®]) should be prescribed and monitored by specialist teams only in light of the EMA statement.

Review date: November 2012

5.0 REFERENCES

- 1 All Wales Medicines Strategy Group. AWMSG Medicines Strategy for Wales. Nov 2008. Available at: <http://www.wales.nhs.uk/sites3/Documents/371/Strategy%20Exec%20Summary%20endorsed%20AWMSG%20April08.pdf>. Accessed Oct 2011.
- 2 Sanofi-Aventis Ltd. Dronedarone (Multaq[®]▼). Summary of Product Characteristics. Nov 2009. Available at: <http://www.medicines.org.uk/EMC/medicine/22894/SPC/Multaq+400mg+tablets/>. Accessed Oct 2011.
- 3 General Medical Council. Good practice in prescribing medicines - guidance for doctors. 2006. Available at: http://www.gmc-uk.org/guidance/ethical_guidance/prescriptions_faqs.asp. Accessed Oct 2011.
- 4 European Medicines Agency. European Medicines Agency recommends restricting use of Multaq[®]▼. Sep 2011. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/09/news_detail_001344.jsp&murl=menus/news_and_events/news_and_event_s.jsp&mid=WC0b01ac058004d5c1. Accessed Oct 2011.
- 5 Medicines and Healthcare products Regulatory Agency. Drug Safety Update Volume 5 Issue 3. Oct 2011. Available at: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/index.htm>. Accessed Oct 2011.
- 6 National Institute for Health and Clinical Excellence. Technology appraisal 197. Atrial fibrillation: dronedarone. Aug 2010. Available at: <http://guidance.nice.org.uk/TA197>. Accessed Oct 2011.

Appendix 1. AWMSG criteria for shared care: dronedarone (Multaq[®]▼).

AWMSG criteria	Dronedarone (Multaq [®] ▼)	Recommendation meets AWMSG criteria for shared care?
Therapy is for a licensed indication for a chronic condition. Occasionally a drug that has a recognised (but unlicensed) indication may be considered suitable for shared care.	<p>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, Multaq[®]▼ should only be prescribed after alternative treatment options have been considered.</p> <p>Should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.</p>	Yes
Statements in the SPC relating to the most appropriate place for prescribing (usually section 4.2) should normally be followed ² .	<p>Treatment should be initiated and monitored only under specialist supervision.</p> <p>Treatment with MULTAQ can be initiated in an outpatient setting.</p>	Yes
There is sufficient evidence for its use over existing preparations. Shared care is therefore not appropriate where clinical experience is limited or side effects have yet to be established.	NICE TA197 ⁶ and MHRA drug safety update ⁵ .	No
The professional signing the prescription takes legal responsibility. Consideration will need to be given to professional opinion, such as that of Drugs and Therapeutics Committee and Local Medical Committee, as to whether shared care of this drug is appropriate.	AWPAG do not consider that shared care would be widely supported by General Practitioners following the EMA statement issued on 22 September 2011 ⁴ .	No
Therapy is initiated and stabilised in secondary/tertiary care. The need for stabilisation will vary with different drugs, patients and local agreement. Adequate follow-up can be provided by secondary/tertiary care.	<p>Previous AWPAG draft (prior to EMA statement⁴) recommended minimum of six months specialist prescribing.</p> <p>Adequate specialist review is essential</p>	
Drug administration and monitoring does not require specialist equipment or skills.	Regular monitoring of cardiovascular, hepatic, renal and pulmonary function.	No

AWMSG criteria	Dronedarone (Multaq [®] ▼)	Recommendation meets AWMSG criteria for shared care?
The safety profile of the drug is such that inadequate monitoring may have serious implications.	SPC listed adverse effects include: Very common*: CCF, raised creatinine, QTc prolonged. Common: bradycardia, GI upset, LFT abnormality, rash, pruritus, fatigue, weakness. Uncommon: interstitial lung disease Rare: hepatocellular liver injury, including life-threatening acute liver failure.	
The service to the patient is convenient and appropriate to their needs.	Survey not undertaken.	
If the patient must attend the specialist on a regular basis (for reasons other than obtaining a prescription) then it may be safer and more appropriate for prescribing to be undertaken by secondary/tertiary care.	Treatment with dronedarone should only be started and monitored by a specialist after other anti-arrhythmic medicines have been considered ⁴ .	Yes
Responsibility for prescribing should remain with consultants where drugs are undergoing or included in a hospital based clinical trial. WHC 91(94).	Not applicable.	Not applicable
A comprehensive shared care protocol for the drug is available that clearly identifies the areas of care for which each partner has responsibility.	Can be met.	Can be met
The use of resources by NHS Wales is efficient. Transferring prescribing between primary and secondary/tertiary care for purely budgetary reasons is not appropriate.	Not a high cost medicine.	Not applicable
SUMMARY: BALANCE OF RESPONSES		NO
<p>* 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).</p> <p>AF: atrial fibrillation; AWPAG: All Wales Prescribing Advisory Group; CCF: congestive cardiac failure; EMA: European Medicines Agency; GI: gastrointestinal; LFT: liver function test; MHRA: Medicines and Healthcare products Regulatory Agency; NICE: National Institute for Health and Clinical Excellence; SPC: Summary of Product Characteristics; TA: technology appraisal; WHC: Welsh Health Circular</p>		

Appendix 2. EMA press release: EMA recommends restricting use of Multaq[®]▼.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 September 2011
EMA/CHMP/718819/2011
Press Office

Press release

European Medicines Agency recommends restricting use of Multaq

Benefit-risk balance of anti-arrhythmic medicine remains positive in a limited population of patients with paroxysmal or persistent atrial fibrillation

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended restricting the use of Multaq. The anti-arrhythmic medicine should only be prescribed for maintaining heart rhythm in patients with paroxysmal or persistent atrial fibrillation for the maintenance of sinus rhythm after successful cardioversion. Due to an increased risk of liver, lung and cardiovascular adverse events, Multaq should only be prescribed after alternative treatment options have been considered. The Committee also recommended a number of other risk minimisation measures to reduce the risk of injuries to liver, lung and cardiovascular system.

Patients who are currently taking Multaq are recommended to have their treatment evaluated by their doctor at their next scheduled appointment.

Multaq (dronedarone) is an anti-arrhythmic medicine. It was authorised in 2009 for use in adults who have had atrial fibrillation in the past or who currently have non-permanent fibrillation.

The review of the overall balance of benefits and risks of Multaq was initiated in January 2011 because of reports of severe liver injury in patients treated with the medicine. During the review the CHMP was informed of the early termination of a clinical trial, the PALLAS study, due to the occurrence of severe cardiovascular side effects such as cardiovascular death, stroke and cardiovascular hospitalisation in patients taking the medicine. The PALLAS study investigated the use of Multaq compared to placebo in patients over 65 years of age with permanent atrial fibrillation and several risk factors. Although Multaq has not been approved for this patient population, the CHMP was concerned about the outcome of the PALLAS study and extended its review to also look at the data relating to cardiovascular safety of the medicine as well as other data that became available on the risk of damage to the lungs.

On the basis of the evaluation of the currently available data, the Committee concluded that there was an increased risk of Multaq causing injury to the liver as well as the lungs when used in accordance with the currently approved prescribing information. The Committee also considered that the

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cardiovascular events shown in the population in the PALLAS study could mean an increased risk of cardiovascular side effects for some patients with non-permanent atrial fibrillation. However, the Committee considered that the availability of a range of treatments for a difficult condition such as atrial fibrillation was important and that for some patients with non-permanent atrial fibrillation Multaq remains a useful treatment option. The CHMP therefore was of the opinion that the benefits of Multaq outweigh its risks in these patients, provided that further changes to the information for prescribers and patients will be introduced to minimise the risk of injury to the liver, lung and heart. These include:

- Treatment with Multaq should be restricted to patients with paroxysmal or persistent atrial fibrillation when sinus rhythm has been obtained. It is no longer indicated for use in patients when atrial fibrillation is still present.
- Treatment with Multaq should only be started and monitored by a specialist after other anti-arrhythmic medicines have been considered.
- Multaq must not be used in patients with permanent atrial fibrillation, heart failure or left ventricular systolic dysfunction (impairment of the left side of the heart).
- Doctors should consider discontinuation of treatment if atrial fibrillation reoccurs.
- Multaq must not be used in patients who have had previous liver or lung injury following treatment with amiodarone, another anti-arrhythmic medicine.
- Patients on Multaq should have their lung and liver function as well as their heart rhythm regularly monitored. Especially the liver function should be closely monitored during the first few weeks of treatment.

The Committee's opinion has now been forwarded to the European Commission for the adoption of a decision.

Notes

1. This press release, together with all related documents, is available on the Agency's website.
2. Multaq has been authorised in the European Union since 26 November 2009 and is marketed in Austria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Ireland, Italy, Lithuania, Malta, Poland, Slovakia, Slovenia, Spain, Sweden and the United Kingdom, as well as in Iceland and Norway.
3. During the assessment the CHMP also received advice from the Scientific Advisory Group on Cardiovascular Issues. This group includes experts in the treatment of cardiovascular diseases and patient representatives. More information is available here:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000025.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028d98&isenabled=true
4. All other opinions and documents adopted by the CHMP at their September 2011 plenary meeting will be published on Friday, 23 September 2011 at 12.00 noon UK time on a dedicated web page.
5. More information on the work of the European Medicines Agency can be found on its website www.ema.europa.eu