4th October 2011

Circular No. P 11/2011

Dear Healthcare Professional,

Re: European Medicines Agency recommends restricting the use of Multaq

Multaq (dronedarone) is an anti-arrhythmic medication which 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.[1] Multaq was authorised in the European Union in 2009 and is currently on the local market.

In January 2011, a review of the overall benefits and risks of Multaq was initiated due to reports of severe liver injury in patients treated with Multaq. Within the course of this review, the PALLAS[1] study, which was undertaken to assess the clinical benefit of dronedarone in patients over 65 years with permanent atrial fibrillation and additional risk factors was prematurely terminated due to a significant excess of cardiac-related deaths as well as cardiovascular hospitalisations and stroke in the dronedarone group. Although Multaq has not been approved for this patient population, the European Medicines Agency (EMA) 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. During the review other data became available on the risk of pulmonary damage with Multaq.

On the basis of the evaluation of the currently available data, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that there was an increased risk of Multaq causing hepatic and pulmonary injury when used in accordance with the currently approved prescribing information. The Committee also considered that the 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. Therefore, the CHMP has recommended:

Medicines Authority
203 Level 3, Rue D'Argens, Gzira, GZR 1368 – Malta.
Tel. (+356) 23439000 Fax. (+356) 23439161 www.medicinesauthority.gov.mt

(1) Restricting the use of this product to those patients with paroxysmal or persistent atrial fibrillation for the maintenance of sinus rhythm after successful cardioversion.

(2) That Multaq should only be prescribed after alternative treatment options have been considered due to the increased risk of liver, lung and cardiovascular adverse events.

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

On the other hand, 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 antiarrhythmic 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 antiarrhythmic medicine.
- Patients on Multaq should have their lung and liver function as well as their heart rhythm regularly monitored. Liver function should be especially closely monitored during the first few weeks of treatment.

Healthcare professionals are encouraged to maintain vigilance on Multaq. Suspected adverse drug reactions may be reported using the Medicines Authority yellow card scheme or online at

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Tel. (+356) 23439000 Fax. (+356) 23439161 www.medicinesauthority.gov.mt

http://www.medicinesauthority.gov.mt/pub/adr.doc or to the marketing authorisation holder or their local representatives. The Committee's opinion has now been forwarded to the European Commission for the adoption of an E.U. wide decision.

The Medicines Authority has participated in the discussions held at the EMA and is in agreement with the full **press release** issued by the EMA, attached here for your perusal. A **question-and-answer** document with more information about the outcome of this assessment is also available.

Healthcare professionals are encouraged to check the Medicines Authority website regularly for product safety updates as these are issued on an ongoing basis.

References

1. MULTAQ Summary of Product Characteristics, available at: *http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/001043/WC500044534.pdf*

2. PALLAS: Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy – Sanofi Aventis, initiated in July 2010

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