

26th July 2011

Information on Multaq (dronedarone) following preliminary study results showing increased cardiovascular risk

Dear Healthcare Professional

• **Summary**

- A clinical study (PALLAS) investigating high risk patients with permanent atrial fibrillation (AF) has been prematurely stopped due to an excess of major cardiovascular (CV) events (cardiovascular death, stroke and cardiovascular hospitalization) in patients receiving dronedarone. The currently available data is preliminary and further advice on the use of dronedarone will be issued in September since results could impact the use in the approved indication.
- In the meantime prescribers are reminded of the current indication: adult clinically stable patients with a history of, or current non-permanent AF to prevent recurrence of AF or to lower ventricular rate.
- Additionally, prescribers are advised to monitor patients regularly in order to ensure that they remain within the authorised indication and do not progress to permanent atrial fibrillation or any of the contraindications for use.
- Prescribers should follow the contraindications and warnings in the Summary of Product Characteristics. In relation to cardiovascular risk the following are particularly relevant:
 - Multaq is contraindicated in patient with bradycardia < 50 beats per minute and in patients in unstable hemodynamic conditions, including patients with symptoms of heart failure at rest or with minimal exertion (corresponding with NYHA class IV and unstable class III patients)
 - Multaq is not recommended in stable patients with NYHA III or LVEF <35%
 - If heart failure develops or worsens, consider the suspension or discontinuation of Multaq.
 - INR should be closely monitored after initiating dronedarone in patients taking vitamin K antagonist as per their label *

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

Further information on the safety concern

The PALLAS study was undertaken to assess clinical benefit of dronedarone 400 mg BID on top of standard therapy in patients with permanent atrial fibrillation and additional risk factors.

In PALLAS, patients with permanent AF were defined by the presence of AF/AFL for at least 6 months prior to randomization and patient and physician decision to allow AF to continue without further efforts to restore sinus rhythm. Patients also had to have additional CV risk factors.

The trial had two composite co-primary endpoints:

1. Major cardiovascular events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death)

* This recommendation is in the process of being added to the Summary of Product Characteristics.

2. Cardiovascular hospitalization or death from any cause.

On July 5th, 2011 the PALLAS Data Monitoring Committee (DMC) reviewed the unblinded data and concluded that there was a significant excess of events in the dronedarone group for both co-primary outcomes as well as cardiovascular hospitalizations (hazard ratio: 1.43; 95% CI: 1.07-1.92), all heart failure events (hazard ratio: 2.53; 95% CI: 1.68-3.82) and stroke (hazard ratio: 2.44; 95% CI: 1.01-5.87). Based on these preliminary figures, the DMC recommended the PALLAS study to be stopped and patients included in the trial were instructed to immediately discontinue study medication.

The benefit-risk balance of Multaq is currently under review by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) and further advice will be issued in September 2011.

Call for reporting:

Please report suspected adverse reactions with Multaq to the MHRA through the Yellow Card Scheme online at www.yellowcard.gov.uk. Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail: "FREEPOST YELLOW CARD"
- at the back of the British National Formulary (BNF)
- by telephoning the Commission of Human Medicines (CHM) free phone line: 0800-731-6789
- or by electronic download through the MHRA website (<http://yellowcard.mhra.gov.uk/downloads/>)

This information may also 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 most current product information (Summary of Product Characteristics) is attached to this letter.

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

Sincerely,



Dr Tony Whitehead
Medical Director
Sanofi-aventis