25th January 2011

Multaq 400mg Film-Coated Tablets EU/1/09/591/001-004

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 can 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 If ALT levels are confirmed to be ≥3 × ULN after re-measurement, dronedarone treatment should be withdrawn.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 the Irish Medicines Board.

- **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 Irish Medicines Board **using the on-line reporting function on the IMB website (www.imb.ie) or alternatively by contacting the IMB at 01 6764971.** In addition, this information may be reported to sanofi-aventis Ireland Ltd., please phone 01-4035600.

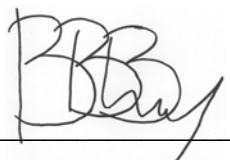
- **Communication information**

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 further questions or require additional information, please also contact our Medical Information Department 01-4035600 or email IEmedinfo@sanofi-aventis.com

Sincerely,



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