IRISH MEDICINES BOARD

Multaq (dronedarone) Association with Severe Liver Injury

Dronedarone is indicated in clinically stable adult 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 cases of acute liver failure requiring transplantation. Some of these cases occurred early after the start of treatment, with the two cases requiring liver transplantation occurring 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.

Following receipt of these reports, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has initiated a review of all available data concerning the possible risks of liver injury associated with the use of dronedarone and their impact on its benefit-risk balance.

The Committee discussed dronedarone during its January 2011 meeting and concluded that there was a need for urgent regulatory action to help manage the possible risk of severe liver complications with the medicine. The Committee recommended the inclusion of warnings and precautions in the medicine's prescribing information, to ensure appropriate monitoring of liver function before initiation of and during treatment with dronedarone, recommending that treatment is stopped if there are signs of potential liver damage.

Further evaluation of the data is continuing in the context of a formal EU wide referral procedure, the outcome of which will be communicated once the CHMP has reached its final opinion.

In the meantime, the new European regulatory recommendations are as follows:

Advice to Healthcare Professionals

- For patients prescribed dronedarone, liver function tests should be performed:
  - prior to initiation of 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 immediately report any signs or symptoms of potential liver injury to their physician. Symptoms of liver injury include sustained new-onset abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine or itching.

The product information (Summary of Product Characteristics [SmPC] and package leaflet) will be revised to include this information. Updated educational materials will be distributed when available.

The current European public assessment report for Multaq can be found on the EMA website: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/001043/WC500044536.pdf

Key message:

Cases of liver injury, including two cases of liver failure requiring transplantation have been reported in patients receiving dronedarone. Some of these cases occurred early after the 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.**

This section has been supplied by the IMB for use in MIMS Ireland. However, the IMB is independent and impartial to any other information contained in this directory