Health Canada Endorsed Important Safety Information on Multaq®

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L'essentiel c'est la santé.

March 10, 2011

Dear Health Care Professional:

Subject: Updated Safety Information for Multaq® (dronedarone) in regards to hepatocellular liver injury

Sanofi-aventis Canada Inc. in collaboration with Health Canada, would like to inform you of important new safety information regarding Multaq (dronedarone).

During the 16 months following initial launch of Multaq (July 20th, 2009), 155 post-marketing cases (87 serious cases) reporting hepatobiliary adverse events, including rare cases of hepatic failure, have been received. Some cases were suspected of drug-induced hepatic injury with a predominant hepatocellular pattern of injury, including two foreign post-marketing case reports of acute hepatic failure requiring transplantation. A definitive causal relationship between Multaq and these cases has not been established.

Exposure to Multaq through September 2010 was estimated at 79,503 patient-years.

Multaq is indicated for the treatment of patients with a history of, or current atrial fibrillation to reduce the risk of cardiovascular hospitalization due to atrial fibrillation.

- Healthcare professionals should discuss with their patients this new important safety information regarding Multaq treatment.
- Patients treated with Multaq should be advised to immediately report symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fatigue, right upper abdominal quadrant pain, jaundice, dark urine, or itching).
- It has not been established that routine periodic monitoring of hepatic enzymes would enable early detection of severe liver injury. However, healthcare professionals should consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment.
- If hepatic injury is suspected, Multaq should be discontinued immediately and followed by necessary blood tests.
- The safety of restarting Multaq in patients who have sustained liver injury from any cause is unknown; accordingly, its use in such patients is not recommended.

The two cases of acute hepatic failure requiring transplantation occurred at 4.5 and 6 months after initiation of Multaq in patients with previously normal hepatic serum enzymes. Both patients were female and approximately 70 years of age.

In the first case, the patient had underlying intermittent atrial fibrillation, arterial hypertension and stable coronary artery disease. She was treated with Multaq for 4.5 months. Two weeks prior to hospitalization she reported increased exhaustion and tiredness. One week prior to admission she discontinued Multaq, and at the time of admission she was noted to have jaundice, coagulopathy, transaminitis and hyperbilirubinemia, which progressed to hepatic encephalopathy over the next nine days. A pre-transplant workup did not reveal another etiology of liver failure.

In the second case, the patient had a medical history of paroxysmal atrial fibrillation and Sjögren's syndrome. Following 6 months of treatment with Multaq, she developed weakness, abdominal pain, coagulopathy, transaminitis and hyperbilirubinemia. She was transplanted 1 month later; no alternate etiology for liver failure was identified in the transplant work-up. In both cases, the explanted liver showed evidence of extensive hepatocellular necrosis.

Sanofi-aventis has been working with Health Canada, and Multaq Product Monograph was revised to include this new safety information.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious hepatocellular liver injury or other serious or unexpected adverse reactions in patients receiving Multaq (dronedarone hydrochloride) should be reported to sanofi-aventis Canada Inc. or Health Canada at the following addresses:

Sanofi-aventis Canada Inc.
2150 St-Elzear Blvd. West
LAVAL, Quebec
H7L 4A8
Telephone: 1-800-267-7927

The Product Monograph and a copy of this Important Safety Information can be accessed online at www.sanofi-aventis.ca

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario K1A 0K9

The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section. The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties.*

For other health product inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: (613) 954-6522
Fax: (613) 952-7738

To change your mailing address or fax number, contact the Market Authorization Holder (Industry).

Sincerely,

original signed by

Monique Furlan, B. Pharm., M. Sc.
Director, Medical Strategy and Regional Operations
sanofi-aventis Canada Inc.