

January 14, 2011

**IMPORTANT
DRUG
WARNING**

sanofi aventis
Because health matters

Hepatic Failure in Patients Treated with Multaq (Dronedarone)

Dear Healthcare Provider:

Sanofi-aventis would like to inform you of several cases of hepatocellular liver injury and hepatic failure in patients receiving Multaq (dronedarone), including two post-marketing reports of acute hepatic failure requiring transplantation. Multaq is indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent history of AF/AFL and associated cardiovascular risk factors (age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter \geq 50 mm or left ventricular ejection fraction <40%) who are in sinus rhythm or who will be cardioverted.

Healthcare professionals should advise patients treated with Multaq to immediately report symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching) and should consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment. It is not known whether routine periodic monitoring of serum enzymes will prevent the development of severe liver injury. If hepatic injury is suspected, Multaq should be promptly discontinued and testing of serum enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase, as well as the serum bilirubin, should be performed to establish whether there is liver injury. If liver injury is found, appropriate treatment should be instituted and investigations should be performed to establish the probable cause. Multaq should not be restarted in patients without another explanation for the observed liver injury.

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 alternative 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 is in communication with the FDA and this issue will be closely reviewed and monitored. The Prescribing Information for Multaq will be revised to include this information and will be distributed once it has been reviewed and approved by the FDA (the link to the *current* Prescribing Information has been provided below for your information). **We encourage you to discuss the new important safety information outlined in this letter with your patients.**

Healthcare professionals should report cases of hepatic injury and failure or any serious adverse events suspected to be associated with the use of Multaq to sanofi-aventis at 1-800-633-1610 (option 2).

Alternatively, report this information to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (<https://www.accessdata.fda.gov/scripts/medwatch/>) or mailed, using the MedWatch for FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Sincerely,

A handwritten signature in cursive script that reads "Paul H. Chew, M.D.".

Paul H. Chew, MD
US Chief Science Officer/Chief Medical Officer
sanofi-aventis U.S.

Click here for full [Prescribing Information, including Boxed Warning](#).
This letter was prepared with the guidance of FDA.

