

December 2011

**IMPORTANT
DRUG
WARNING**



Increased Risk of Death, Stroke and Heart Failure in Patients with Permanent Atrial Fibrillation treated with Multaq (Dronedarone)

Dear Healthcare Provider:

In August 2011, Sanofi communicated preliminary information on the premature termination of the PALLAS (Permanent Atrial fibrillation outcome Study using Dronedarone on top of standard therapy) study due to increased risk of CV death, stroke, and heart failure events.

Following adjudication and final analysis of the PALLAS data and subsequent update and FDA-approval of the United States Prescribing Information (USPI), Sanofi would like to provide you with highlights of the important updates to the Multaq USPI pertaining to PALLAS and permanent atrial fibrillation (AF).

In addition to an update to the heart failure contraindication, the boxed warning for Multaq has been expanded to include permanent AF (AF patients who will not or cannot be cardioverted into normal sinus rhythm). The boxed warning now reads as follows:

**WARNING:
INCREASED RISK OF DEATH, STROKE AND HEART FAILURE IN
PATIENTS WITH DECOMPENSATED HEART FAILURE OR PERMANENT
ATRIAL FIBRILLATION**

MULTAQ is contraindicated in patients with symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure. MULTAQ doubles the risk of death in these patients.

MULTAQ is contraindicated in patients in atrial fibrillation (AF) who will not or cannot be cardioverted into normal sinus rhythm. In patients with permanent AF, MULTAQ doubles the risk of death, stroke, and hospitalization for heart failure.

The following has also been added to the **WARNINGS AND PRECAUTIONS** section of the Multaq USPI:

5 WARNING AND PRECAUTIONS

5.2 Cardiovascular Death and Heart Failure in Permanent AF

MULTAQ doubles the risk of cardiovascular death (largely arrhythmic) and heart failure events in patients with permanent AF. Patients treated with dronedarone

should undergo monitoring of cardiac rhythm no less often than every 3 months. Cardiovert patients who are in atrial fibrillation (if clinically indicated) or discontinue MULTAQ. MULTAQ offers no benefit in subjects in permanent AF.

5.3 Increased Risk of Stroke in Permanent AF

In a placebo-controlled study in patients with permanent atrial fibrillation, dronedarone was associated with an increased risk of stroke, particularly in the first two weeks of therapy. MULTAQ should only be initiated in patients in sinus rhythm who are receiving appropriate antithrombotic therapy.

Additionally, the indication for Multaq has been updated to help ensure its appropriate use in paroxysmal or persistent atrial fibrillation (i.e. non-permanent AF patients).

Multaq is indicated to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation (AF).

In accordance with these changes, the Multaq Medication Guide has been updated to include this information. **We encourage you to discuss the new important safety information outlined in this letter and the updated Multaq USPI and Medication Guide with your patients** (the link to the current Prescribing Information, including Medication Guide, has been provided below for your review).

Also of note, Sanofi is collaborating with the FDA to appropriately update the Multaq Risk Evaluation and Mitigation Strategy (REMS). You will be notified of the changes to the Multaq REMS program once it is FDA-approved.

Please note the information above does not contain all changes to the Multaq USPI. Please refer to the full Prescribing Information for Multaq for complete details.

For additional information, please contact Sanofi Medical Information Services at 1-800-633-1610 (option 1). Healthcare professionals should report adverse events suspected to be associated with the use of Multaq to Sanofi 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,



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.

**IMPORTANT
DRUG
WARNING**



Increased Cardiovascular Risk in Permanent AF Patients Treated with Multaq® (dronedarone)

Dear Healthcare Provider:

Sanofi-aventis, US LLC would like to inform you of the premature discontinuation of the PALLAS (Permanent Atrial fibrillation outcome Study using Dronedarone on top of standard therapy) phase IIIb clinical trial due to an excess of cardiovascular death, stroke and cardiovascular hospitalization, primarily heart failure hospitalization, in those patients receiving dronedarone. This indication-seeking trial enrolled patients with permanent atrial fibrillation (AF), a different, but related, population than that for which Multaq is indicated. Permanent AF was defined by the presence of AF/atrial flutter (AFL) for at least 6 months prior to randomization and patient/physician decision to allow AF to continue without further efforts to restore sinus rhythm. The trial had two composite co-primary endpoints: 1). Major cardiovascular events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death); 2). Cardiovascular hospitalization or death from any cause. The currently available data from the PALLAS trial is preliminary; a full and comprehensive analysis of these data is ongoing.

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.

Multaq should not be prescribed for patients with permanent AF. Healthcare professionals are advised to monitor patients regularly (at least every six months) in order to ensure that they remain within the approved indication and do not progress to permanent atrial fibrillation or new or worsening heart failure. Additionally, please be aware of, and refer to, the **BOXED WARNING**, **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS** sections of the Multaq Prescribing Information for further information about the appropriate patient population.

Sanofi-aventis is in communication with the FDA and additional analyses are being conducted. 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). For additional information, please contact sanofi-aventis Medical Information Services at 1-800-633-1610 (option 1).

Healthcare professionals should report 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." followed by a period.

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.

**IMPORTANT
DRUG
WARNING**



Hepatic Failure in Patients Treated with Multaq (Dronedarone)

Dear Healthcare Provider:

The purpose of this letter is to inform you of new important safety information for Multaq[®], an antiarrhythmic. Multaq[®] was approved in July 2009 with an FDA required Risk Evaluation and Mitigation Strategy (REMS). The REMS has been modified to include informing healthcare professionals and patients about the serious risks of liver injury and hepatic failure with Multaq[®].

Several cases of hepatocellular liver injury and hepatic failure have occurred 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.

The Prescribing Information for Multaq has been revised to include this information (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.