NDA 22-425 Multaq® (dronedarone)

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

- To prevent Multaq® use in patients with:
  - Symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure
  - Permanent atrial fibrillation (AF) that will not or cannot be cardioverted into normal sinus rhythm
- To inform healthcare professionals about the serious risks of Multaq®, including:
  - Increased risk of cardiovascular death in patients with symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure
  - Increased risk of cardiovascular death, heart failure and stroke in patients with permanent AF
  - Signs and symptoms of liver injury and hepatic failure

II. REMS ELEMENTS

A. COMMUNICATION PLAN

Sanofi-aventis will implement a Communication Plan to inform healthcare professionals (HCPs) of the risks associated with the use of Multaq®, safe and appropriate prescribing information, and the goals of the REMS.

The Communication Plan includes:

1. Healthcare Professional Information Sheet
   a. The Healthcare Professional Information Sheet is intended to highlight the important safety information for Multaq. The Information Sheet provides a high-level reminder for HCPs for each point of the prescribing process: initiation of therapy, patient counseling and ongoing management and follow-up. This sheet thereby re-enforces the goals of the
REMS and actions to ensure appropriate use. The Healthcare Professional Information Sheet will be posted on the REMS website within 15 days and continue for a period of 5 years after drug approval.

The Healthcare Professional Information Sheet is a part of the REMS and is appended.

2. Dear Healthcare Provider Letters

a. Important drug warning about increased risk of death, stroke and heart failure in patients with permanent atrial fibrillation treated with Multaq®. This Dear Healthcare Provider letter provided an update to an important drug warning about the increased risk of cardiovascular events and death in patients with permanent AF treated with Multaq®. Additionally, the need to discontinue Multaq® in patients who develop or progress toward permanent AF while on Multaq® was highlighted. This DHCP letter was posted on the REMS website (www.multaqrems.com) within 15 days after the approval of the permanent AF REMS modification (June 2012) and will continue for a period of 1 year from approval of that REMS modification (June 2013).

The Dear Healthcare Provider letter (permanent AF) is part of the REMS and is appended.

b. Important drug warning about hepatic failure in patients treated with Multaq®. This Dear Healthcare Provider letter provided an important drug warning about hepatic failure in patients treated with Multaq® and the signs and symptoms that both HCPs and patients should monitor. This DHCP letter was posted on the REMS website (www.multaqrems.com) within 15 days after the approval of the hepatic REMS modification (August 2011) and will continue for 1 year after the corresponding REMS modification approval (August 2012).

The Dear Healthcare Provider letter (hepatic) is part of the REMS and is appended.

3. Healthcare Provider Checklist

a. Sanofi-aventis will post the updated prescriber checklist, which provides key evaluation points for the HCP at the point of prescribing, to the REMS website within 15 days of this REMS modification approval. The Checklist will assist the HCP in the identification of contraindications for use as well as highlight the warnings and precautions for use when considering treatment with Multaq®. The Healthcare Provider Checklist will also be made available via sales and/or medical representatives and through the Sponsor’s Medical Information Services Department.

The updated Healthcare Provider Checklist is part of the REMS and is appended.

4. REMS Print Advertising in Professional Society Journals

a. Sanofi-aventis issued REMS Print Advertisements for approximately 30 months in each of the following professional society journals since product approval:

i. Journal of the American College of Cardiology

ii. Circulation

iii. Annals of Internal Medicine
REMS Print Advertisements have been discontinued as the 24 month commitment was met.

5. *The REMS website*

   a. Sanofi-aventis will ensure the REMS webpage, www.multaqrems.com, includes a link to the updated REMS materials as well as the two following FDA Drug Safety Communications: Severe liver injury associated with the use of dronedarone (marketed as Multaq) [1/14/2011] and Review update of Multaq (dronedarone) and increased risk of death and serious cardiovascular adverse events [12/19/2011]. The REMS webpage will be available for 5 years after drug approval.

   The modified REMS website is part of the REMS and is appended.

B. **TIMETABLE FOR SUBMISSION OF ASSESSMENTS**

Sanofi-aventis will submit REMS Assessments to the FDA annually for years 1-5 and at year 7. Assessment reports are due on the 31st of December. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for the assessment. Sanofi-aventis will submit each assessment so that it will be received by the FDA on or before the due date.