DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22425/S-016, S-017, S-018 **SUPPLEMENT APPROVAL**

sanofi-aventis U.S., LLC
Attention: Nilda Ramos, MS
Manager, Global Regulatory Affairs
200 Crossing Boulevard
Mailstop: BX2-712C
Bridgewater, NJ 08807

Dear Ms. Ramos:

Please refer to your Supplemental New Drug Applications (sNDA) dated March 22, (S-016 and S-017), and July 11, 2012 (S-018), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Multaq (dronedarone hydrochloride) 400 mg Tablets.

We acknowledge receipt of your amendments dated July 10 (S-017) and 11 (S-016), 2012, and your risk evaluation and mitigation strategy (REMS) assessment dated August 29, 2011.

These "Prior Approval" supplemental new drug applications provide for labeling revised as described below for S-016, S-017, and S-018, and a proposed modification to the approved risk evaluation and mitigation strategy (REMS) for S-017.

S-016

Highlights of Prescribing Information

1. Under Recent Major Changes, a new bullet has been added for the addition of lung toxicity to Contraindications and Warnings and Precautions.

2. In seventh bullet under Contraindications, "Liver toxicity…" has been changed to "Liver or lung toxicity..."

3. Under Contraindications, the following information has been added as a new bullet:

   Hypersensitivity to the active substance or to any of the excipients (4)

4. Under Warnings and Precautions, the following information has been added as a new bullet to reflect the addition of a new warning regarding Pulmonary Toxicity (in addition, bullets listed after Pulmonary Toxicity have been renumbered throughout the label, and the Liver Injury bullet has been repositioned based on its position in the Full Prescribing Information):

   If pulmonary toxicity is confirmed, discontinue treatment (5.6)

5. Under Drug Interactions, the first bullet has been changed from:

   Antiarrhythmics: Avoid concomitant use (4, 7.1)

To:

Class I or III Antiarrhythmics: contraindicated (4, 7.1)

Full Prescribing Information: Contents

6. "WARNINGS" has been changed to "WARNING" in the header.

7. Under Warnings and Precautions, a new sub-section 5.6 has been added for Pulmonary Toxicity (subsequent sub-sections have been renumbered)

Full Prescribing Information

8. In seventh bullet under Contraindications, "Liver toxicity…" has been changed to "Liver or lung toxicity..."

9. Under Contraindications, the following information has been added as a new bullet:

   Hypersensitivity to the active substance or to any of the excipients (4)

10. Under Warnings and Precautions, the following new sub-section has been added:

    5.6 Pulmonary Toxicity

    Cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported in patients treated with MULTAQ in the post-marketing setting *[see Adverse Reactions (6.2)]*. Onset of dyspnea or non-productive cough may be related to pulmonary toxicity and patients should be carefully evaluated clinically. If pulmonary toxicity is confirmed, MULTAQ should be discontinued.

11. Under Adverse Reactions, the following has been added as a new bullet:

    Pulmonary toxicity *[see Warnings and Precautions (5.6)]*

12. Under Adverse Reactions/Postmarketing Experience, the Respiratory listing has been changed from:

    Respiratory: Postmarketing cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported.

    To:

    Respiratory: Interstitial lung disease including pneumonitis and pulmonary fibrosis *[see Warnings and Precautions (5.6)]*

13. Under Adverse Reactions/Postmarketing Experience, the following has been added:

    Immune: Anaphylactic reactions including angioedema

S-017

Medication Guide

1. Under "Who should not take MULTAQ," the following information has been added:

   You are allergic to dronedarone or any of the other ingredients in MULTAQ. See the end of this Medication Guide for a complete list of ingredients in MULTAQ.

2. Under "Before taking MULTAQ, tell your doctor if you," "Have" has been changed to "have."

3. Under "What are the possible side effects of MULTAQ," the following information has been added:

   Inflammation of the lungs, including scarring and thickening. Call your doctor if you develop shortness of breath or a dry cough during treatment with MULTAQ.

S-018

Full Prescribing Information

1. Under Adverse Reactions/Postmarketing Experience, the following has been added:

   Vascular: Vasculitis, including leukocytoclastic vasculitis

2. Under Drug Interactions/Pharmacodynamic Interactions, the Digoxin section has been changed from:

   Digoxin can potentiate the electrophysiologic effects of dronedarone (such as decreased AV-node conduction). In clinical trials, increased levels of digoxin were observed when dronedarone was co-administered with digoxin. Gastrointestinal disorders were also increased. Consider the need for continued digoxin therapy. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

   To:

   In the ANDROMEDA (patients with recently decompensated heart failure) and PALLAS (patients with permanent AF) trials baseline use of digoxin was associated with an increased risk of arrhythmic or sudden death in dronedarone-treated patients compared to placebo. In patients not taking digoxin, no difference in risk of sudden death was observed in the dronedarone vs. placebo groups. [See Clinical Trials (14.3)]).

   Digoxin can potentiate the electrophysiologic effects of dronedarone (such as decreased AV-node conduction). Dronedarone increases exposure to digoxin [see Drug Interactions (7.3), Clinical Pharmacology (12.3)].

   Consider discontinuing digoxin. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity.

3. Under Drug Interactions/Effects of Dronedarone on Other Drugs/P-glycoprotein substrates/Digoxin, the second sentence has been changed from:

   Consider the need for continued digoxin therapy.

   To:

Consider discontinuing digoxin.

4. Under Clinical Studies/ANDROMEDA, the following information has been added:

   Baseline digoxin therapy was reported in 6/16 dronedarone patients vs. 1/16 placebo patients who died of arrhythmia. In patients without baseline use of digoxin, no excess risk of arrhythmic death was observed in the dronedarone vs. placebo groups.

5. Under Clinical Studies/PALLAS, the first bullet has been changed from:

   Mortality: 25 dronedarone vs. 13 placebo (HR, 1.94; CI, 0.99 to 3.79). The majority of deaths in the dronedarone group were classified as arrhythmic/sudden deaths (HR, 3.26; CI: 1.06 to 10.0). Baseline digoxin therapy was reported in 11/13 dronedarone patients who died of arrhythmia. None of the arrhythmic deaths on placebo (4) reported use of digoxin.

   To:

   Mortality: 25 dronedarone vs. 13 placebo (HR, 1.94; CI, 0.99 to 3.79). The majority of deaths in the dronedarone group were classified as arrhythmic/sudden deaths (HR, 3.26; CI: 1.06 to 10.0) *[See Drug Interactions (7.1)]*. Baseline digoxin therapy was reported in 11/13 dronedarone patients who died of arrhythmia. None of the arrhythmic deaths on placebo (4) reported use of digoxin. In patients without baseline use of digoxin, no excess risk of arrhythmic death was observed in the dronedarone vs. placebo groups.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and REMS.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft

Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Multaq (dronedarone hydrochloride) was originally approved on July 1, 2009, and REMS modifications were approved on February 11, 2011, August 5, 2011, and June 13, 2012. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of:

- Revisions to the Healthcare Provider Checklist (part of the communication plan) to include new risk information regarding hypersensitivity and lung toxicity.
- Revisions to the REMS document, to clarify content
- Revisions to the Medication Guide to include risk information regarding hypersensitivity and lung toxicity.

Your proposed modified REMS, submitted on July 10, 2012, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on July 1, 2009.

The REMS assessment plan will remain the same as that approved on June 13, 2012.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022425 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 022425 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022425
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022425
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
09/07/2012