DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-425 **NDA APPROVAL**

sanofi-aventis U.S., LLC
Attention: Marsha Miller, Ph.D.
Assistant Director, Regulatory Development
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Miller:

Please refer to your new drug application (NDA) dated June 27, 2008, received July 31, 2008, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Multaq (dronedarone hydrochloride) Tablets 400 mg.

We acknowledge receipt of your submissions dated August 14, 15, October 17, 27, 31, November 3, 10, 11, 14, 20, December 2, 3, 10, 17, 19, 24, 2008, and January 22, 28, , 30, February 5, 9, 13, 19, 23, 26, 27, March 10, April 3, 24, 29, May 1, 4, 5, 18, 19, June 4, 10, and 25, 2009.

This new drug application provides for the use of Multaq (dronedarone hydrochloride) Tablets to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-425**." Approval of this submission by FDA is not required before the labeling is used.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper

copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-425**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because of the rarity of AF/AFL in the pediatric population, the geographical dispersion of such patients, and the disparate causes of the condition in such patients.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of lung toxicity, severe skin reactions, or neuropathies, all concerns raised by the effect of the related molecule amiodarone, or to identify use of Multaq (dronedarone hydrochloride) in patients for whom its use is contraindicated.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following according to the timetables in your June 25, 2009, submission:

1. An assessment of spontaneous reports of lung toxicity associated with Multaq (dronedarone hydrochloride). Following approval, and according to the following timetable, submit a yearly report (containing both interval-based and comprehensive data) analyzing spontaneous adverse event reports received that describe lung toxicity. Specialized follow-up (using forms included in your June 4, 2008, submission) should be obtained on these cases to collect additional information on the event (e.g., symptoms, medical history, concomitant medications, laboratory evaluations, imaging results, biopsy results).

Interim Report Submissions:	September 2010
	September 2011
	September 2012
	September 2013
	September 2014
Final Report Submission:	September 2016

2. Conduct an epidemiologic study using claims or electronic health records data to evaluate the potential association between Multaq (dronedarone hydrochloride) use and lung toxicities. Following approval and according to the following timeline, submit a yearly report (containing both interval-based and comprehensive data) on the incidence rate of lung toxicity in Multaq (dronedarone hydrochloride) users vs. non-Multaq (dronedarone hydrochloride) users.

Submission of Final Study Plan:	September 2009
Interim Report Submissions:	December 2010
	December 2011
	December 2012
	December 2013
	December 2014
Final Report Submission:	December 2016

3. Conduct an epidemiologic study using claims or electronic health records data to evaluate the potential association between Multaq (dronedarone hydrochloride) use and neuropathies (including optic neuropathy). Following approval and according to the following timeline, submit a yearly report (containing both interval-based and comprehensive data) on the incidence rate of neuropathies in Multaq (dronedarone hydrochloride) users vs. non-Multaq (dronedarone hydrochloride) users.

Submission of Final Study Plan:	September 2009
Interim Report Submissions:	December 2010
	December 2011
	December 2012
	December 2013
	December 2014
Final Report Submission:	December 2016

4. Conduct an epidemiologic study using claims or electronic health records data to evaluate the potential association between Multaq (dronedarone hydrochloride) use and severe skin reactions. Following approval and according to the following timeline, submit a yearly report (containing both interval-based and comprehensive data) on the incidence rate of severe skin reactions in Multaq (dronedarone hydrochloride) users vs. non-Multaq (dronedarone hydrochloride) users.

Submission of Final Study Plan:	September 2009
Interim Report Submissions:	December 2010
	December 2011
	December 2012
	December 2013
	December 2014
Final Report Submission:	December 2016

5. Conduct an epidemiologic study using claims or electronic health records data to evaluate the use of Multaq (dronedarone hydrochloride) in patients for whom its use is contraindicated. Following approval and according to the following timeline, submit a yearly report (containing both interval-based and comprehensive data) to determine the

extent of dronedarone use in patients for whom its use is contraindicated (for example, patients who have been hospitalized for decompensated heart failure in the 30 days preceding dronedarone initiation).

Submission of Final Study Plan:	September 2009
Interim Report Submissions:	December 2010
	December 2011
	December 2012
	December 2013
	December 2014
Final Report Submission:	December 2016

In your June 25, 2009, submission you agreed that will conduct these 5 studies according to the above timetables.

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on June 10, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

1. Periodic surveys of healthcare professionals to monitor the effectiveness of the interventions in educating prescribers on the goals of the REMS and to monitor appropriate prescribing of Multaq (dronedarone hydrochloride)

2. Periodic surveys of patients to monitor the effectiveness of the interventions in educating patients on the safe and appropriate use of Multaq (dronedarone hydrochloride)

3. A postmarketing epidemiologic study of Multaq (dronedarone hydrochloride) will be conducted in a claims database to assess drug utilization by inappropriate patient (contraindicated) population.

4. Patients' understanding of the serious risks of Multaq (dronedarone hydrochloride)

5. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

6. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

You should submit the final methodology and content of the patient survey at least 90 days prior to initiation of the survey.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that 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.

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

NDA 22-425 - REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22-425
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 22-425
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

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

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures: Agreed-upon labeling and REMS

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

/s/

Robert Temple

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