DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022425/S-013

SUPPLEMENT APPROVAL

sanofi-aventis U.S. LLC
Attention: Nilda M. Ramos, MS
Manager, Global Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Ms. Ramos:

Please refer to your Supplemental New Drug Application (sNDA) S-013 dated and received August 23, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Multaq (Dronedarone hydrochloride) 400 mg Tablets.

We acknowledge receipt of your amendment dated December 13, 2011.

(b) (4)

"Prior Approval" supplemental drug application S-013 provides for labeling revised as follows:

1. In **HIGHLIGHT**S and FULL PRESCRIBING INFORMATION, the boxed warning was changed from:

> **WARNING:**
> **HEART FAILURE**
>
> MULTAQ is contraindicated in patients with NYHA Class IV heart failure or NYHA Class II – III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic **(4).**
>
> In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA Study), patients given dronedarone had a greater than two-fold increase in mortality. Such patients should not be given dronedarone (14.3).

To:

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 heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure. MULTAQ doubles the risk of death in these patients (4, 5.1, 14.3).

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. (4, 5.2,14.4)

2. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the section now reads:

RECENT MAJOR CHANGES ----------

- Warnings and Precautions, Liver Injury (5.5) 02/2011
- Warnings and Precautions Increase in Creatinine after Treatment Initiation (5.8) 08/2011
- Indications and Usage, (1), Contraindications (4), Warnings and Precautions (5.1, 5.2, 5.3, 5.4) 12/2011

3. In **HIGHLIGHTS/CONTRAINDICATIONS**, the section was changed from:

- Class IV heart failure or symptomatic heart failure with a recent decompensation (Boxed Warning, 4)
- Second- or third- degree atrioventicular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker) (4)
- Bradycardia <50 bpm (4)
- Concomitant use of a strong CYP3A inhibitor (4)
- Concomitant use of drugs or herbal products that prolong the QT interval and may induce Torsade de Pointes (4)

- Severe hepatic impairment (4)
- QTc Bazett interval ≥500 ms (4)
- Pregnancy (4, 8.1) and
- Nursing mothers (4, 8.3)

To:

- Permanent AF (patients in whom normal sinus rhythm will not or cannot be restored) (Boxed Warning, 4)
- Recently decompensated heart failure requiring hospitalization or Class IV heart failure. (Boxed Warning, 4)
- Second- or third- degree atrioventicular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker) (4)
- Bradycardia <50 bpm (4)
- Concomitant use of a strong CYP3A inhibitor (4)
- Concomitant use of drugs or herbal products that prolong the QT interval and may induce Torsade de Pointes (4)
- Liver toxicity related to the previous use of amiodarone (4)
- Severe hepatic impairment (4)
- QTc Bazett interval ≥500 ms (4)
- Pregnancy (4, 8.1) and Nursing mothers (4, 8.3)

4. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the section was changed from:
    - Heart failure: If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ (5.1)
    - Liver injury: if hepatic injury is suspected, discontinue MULTAQ (5.2)
    - Hypokalemia and hypomagnesemia: Maintain potassium and magnesium levels within the normal range (5.3)
    - QT prolongation: Stop MULTAQ if QTc Bazett ³500ms (5.4)
    - Increase in creatinine: Monitor serum creatinine periodically (5.5)
    - Teratogen: Women of childbearing potential should use effective contraception while using MULTAQ (5.6)

To:

- Determine cardiac rhythm at least once every 3 months. If AF is detected discontinue MULTAQ or cardiovert (5.1).
- Liver injury: if hepatic injury is suspected, discontinue MULTAQ (5.5)
- Ensure appropriate antithrombotic therapy prior to and throughout MULTAQ use. (5.3)
- Hypokalemia and hypomagnesemia: Maintain potassium and magnesium levels within the normal range (5.6)
- Increase in creatinine: Monitor serum creatinine periodically (5.8)
- Teratogen: Women of childbearing potential should use effective

contraception while using MULTAQ (5.9)

5. In **HIGHLIGHTS/DRUG INTERACTIONS**, the section was changed from:

Dronedarone is metabolized by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6 and has potentially important pharmacodynamic interactions (7)
• Antiarrhythmics: Avoid concomitant use (4, 7.1)
• Digoxin: Consider discontinuation or halve dose of digoxin before treatment and monitor (7.1, 7.3)
• Calcium channel blockers (CCB): Initiate CCB with low dose and increase after ECG verification of tolerability (7.1,7.2, 7.3)
• Beta-blockers: May provoke excessive bradycardia, Initiate with low dose and increase after ECG verification of tolerability (7.1, 7.3)
• CYP 3A inducers: Avoid concomitant use (7.2)
• Grapefruit juice: Avoid concomitant use (7.2)
• Statins: Follow label recommendations for concomitant use of certain statins with a CYP 3A and P-gP inhibitor like dronedarone (7.3)
• CYP 3A substrates with a narrow therapeutic index (e.g., sirolimus and tacrolimus): Monitor and adjust dosage of concomitant drug as needed when used with MULTAQ (7.3)
• Warfarin: Monitor INR after initiating dronedarone in patients taking warfarin. (7.3)

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Dronedarone is metabolized by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6 and has potentially important pharmacodynamic interactions (7)
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- Digoxin: Consider discontinuation or halve dose of digoxin before treatment and monitor digoxin levels (7.1, 7.3)
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- CYP 3A substrates with a narrow therapeutic index (e.g., sirolimus and tacrolimus): Monitor and adjust dosage of concomitant drug as needed when used with MULTAQ (7.3)
- Warfarin: Monitor INR after initiating dronedarone in patients taking warfarin. (7.3)

6. Under **CONTRAINDICATIONS**, the following section was changed from:

MULTAQ is contraindicated in patients with:
• NYHA Class IV heart failure or NYHA Class II – III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic *[see Boxed Warning and Clinical Studies (14.3)]*
• Second- or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
• Bradycardia <50 bpm
• Concomitant use of strong CYP 3A inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, and ritonavir *[see Drug Interactions (7.2)]*
• Concomitant use of drugs or herbal products that prolong the QT interval and might increase the risk of Torsade de Pointes, such as phenothiazine anti-psychotics, tricyclic antidepressants, certain oral macrolide antibiotics, and Class I and III antiarrhythmics
• QTc Bazett interval ³500 ms or PR interval >280 ms
• Severe hepatic impairment
• Pregnancy (Category X): MULTAQ may cause fetal harm when administered to a pregnant woman. MULTAQ is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.
• Nursing mothers *[see Use in Specific Populations (8.3)]*

To:

MULTAQ is contraindicated in patients with:

- Permanent atrial fibrillation (patients in whom normal sinus rhythm will not or cannot be restored) *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV symptoms *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Second- or third-degree atrioventricular (AV) block, or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Bradycardia <50 bpm
- Concomitant use of strong CYP 3A inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, and ritonavir *[see Drug Interactions (7.2)]*
- Concomitant use of drugs or herbal products that prolong the QT interval and might increase the risk of Torsade de Pointes, such as phenothiazine anti-

psychotics, tricyclic antidepressants, certain oral macrolide antibiotics, and Class I and III antiarrhythmics
- Liver toxicity related to the previous use of amiodarone
- QTc Bazett interval ≥500 ms or PR interval >280 ms
- Severe hepatic impairment
- Pregnancy (Category X): MULTAQ may cause fetal harm when administered to a pregnant woman. MULTAQ is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.
- Nursing mothers *[see Use in Specific Populations (8.3)]*

7. Under **WARNINGS AND PRECAUTIONS**, the section was changed from:

5.1 Patients with New or Worsening Heart Failure during Treatment

Postmarketing cases of new onset and worsening heart failure have been reported during treatment with Multaq. Advise patients to consult a physician if they develop signs or symptoms of heart failure such as weight gain, dependent edema, or increasing shortness of breath. If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ.

5.2 Liver Injury

Hepatocellular liver injury, including acute liver failure requiring transplant, has been reported in patients treated with MULTAQ in the post-marketing setting. Advise patients treated with MULTAQ to report immediately symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching). 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, promptly discontinue MULTAQ and test serum enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase, as well as serum bilirubin, to establish whether there is liver injury. If liver injury is found, institute appropriate treatment and investigate the probable cause. Do not restart MULTAQ in patients without another explanation for the observed liver injury.

5.3 Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics

Hypokalemia or hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics. Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ.

5.4 QT Interval Prolongation

Dronedarone induces a moderate (average of about 10 ms but much greater effects have been observed) QTc (Bazett) prolongation *[see Clinical Pharmacology (12.2) and Clinical Studies (14.1)]*. If the QTc Bazett interval is ≥500 ms, MULTAQ should be stopped *[see Contraindications (4)]*.

5.5 Increase in Creatinine after Treatment Initiation

Small increases in creatinine levels (about 0.1 mg/dL) following dronedarone treatment initiation have been shown to be a result of inhibition of creatinine's tubular secretion.

The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation.

Larger increases in creatinine after dronedarone initiation have been reported in the postmarketing setting. Some cases also reported increases in blood urea nitrogen. In most cases, these effects appear to be reversible upon drug discontinuation. Monitor renal function periodically.

5.6 Women of Childbearing Potential

Premenopausal women who have not undergone a hysterectomy or oophorectomy must use effective contraception while using MULTAQ. Dronedarone caused fetal harm in animal studies at doses equivalent to recommended human doses. Women of childbearing potential should be counseled regarding appropriate contraceptive choices taking into consideration their underlying medical conditions and lifestyle preferences *[see Use in Specific Populations (8.1)]*.

To:

5.1 Cardiovascular Death in NYHA Class IV or Decompensated Heart Failure

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

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 [*see Clinical Studies (14.4)*]. MULTAQ should only be initiated in patients in sinus rhythm who are receiving appropriate antithrombotic therapy [*see Drug interactions (7.3)*].

5.4 New Onset or Worsening Heart Failure

New onset or worsening of heart failure has been reported during treatment with MULTAQ in the postmarketing setting. In a placebo controlled study in patients with permanent AF increased rates of heart failure were observed in patients with normal left ventricular function and no history of symptomatic heart failure, as well as those with a history of heart failure or left ventricular dysfunction.

Advise patients to consult a physician if they develop signs or symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath. If heart failure develops or worsens and requires hospitalization, discontinue MULTAQ.

5.5 Liver Injury

Hepatocellular liver injury, including acute liver failure requiring transplant, has been reported in patients treated with MULTAQ in the post-marketing setting. Advise patients treated with MULTAQ to report immediately symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching). Consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment, but it is not known whether routine periodic monitoring of serum enzymes will prevent the development of severe liver injury. If hepatic injury is suspected, promptly discontinue MULTAQ and test serum enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase, as well as serum bilirubin, to establish whether there is liver injury. If liver injury is found, institute appropriate treatment and investigate the probable cause. Do not restart MULTAQ in patients without another explanation for the observed liver injury.

5.6 Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics

Hypokalemia or hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics. Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ.

5.7 QT Interval Prolongation

Dronedarone induces a moderate (average of about 10 ms but much greater effects have been observed) QTc (Bazett) prolongation [see Clinical Pharmacology (12.2) and Clinical Studies (14.1)]. If the QTc Bazett interval is ≥500 ms, discontinue MULTAQ [see Contraindications (4)].

5.8 Increase in Creatinine after Treatment Initiation
Small increases in creatinine levels (about 0.1 mg/dL) following dronedarone treatment initiation have been shown to be a result of inhibition of creatinine's tubular secretion. The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation. Larger increases in creatinine after dronedarone initiation have been reported in the post-marketing setting. Some cases also reported increases in blood urea nitrogen. In most cases, these effects appear to be reversible upon drug discontinuation. Monitor renal function periodically.

5.9 Women of Childbearing Potential
Premenopausal women who have not undergone a hysterectomy or oophorectomy must use effective contraception while using MULTAQ. Dronedarone caused fetal harm in animal studies at doses equivalent to recommended human doses. Counsel women of childbearing potential regarding appropriate contraceptive choices. *[see Use in Specific Populations (8.1)]*.

8. Under **ADVERSE REACTIONS/Post Marketing Experience**, the following text was added:

Cardiac: New or worsening heart failure *[see Warnings and Precautions (5.3)]*

Hepatic: Liver Injury *[see Warnings and Precautions (5.5)]*

9. Under **DRUG INTERACTIONS/Pharmacodynamic Interactions/Digoxin**, the paragraph now reads:

Digoxin
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. Because of the pharmacokinetic interaction *[see Drug Interaction (7.3)]* and possible pharmacodynamic interaction, 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.

10. Under **CLINICAL STUDIES**, a new section was added:

14.4 PALLAS

Patients with permanent AF (AF documented in 2 weeks prior to randomization and at least 6 months prior to randomization in whom cardioversion had failed or was not planned) and additional risk factors for thromboembolism (coronary artery disease, prior stroke or TIA, symptomatic heart failure, LVEF <40%,

peripheral arterial occlusive disease, or age >75 with hypertension and diabetes) were randomized to dronedarone 400 mg twice daily or placebo.
After enrollment of 3236 patients (placebo=1617 and dronedarone=1619) and a median follow up of 3.7 months days for placebo and 3.9 for dronedarone, the study was terminated because of a significant increase in

- 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.
- Stroke: 23 dronedarone vs. 10 placebo (HR, 2.32; CI: 1.11 to 4.88). The increased risk of stroke observed with dronedarone was observed in the first two weeks of therapy (10 dronedarone vs. 1 placebo), most of the subjects treated with dronedarone did not have an INR of 2.0 to 3.0.[*see Warning and Precaution (5.3)*]
- Hospitalizations for heart failure in the dronedarone group: 43 dronedarone vs. 24 placebo (HR, 1.81; CI: 1.10 to 2.99).

11. Throughout the label, the cross references were updated to reflect the changes made.

12. There are other agreed-upon editorial changes reflected in the attached labeling

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We have completed our review of this supplemental application, as amended, and 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, 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 (text for the package insert, text for the patient package insert, Medication Guide), 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.

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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

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D
Deputy Director for Safety
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
12/19/2011