NDA 22425/S-002

SUPPLEMENT APPROVAL

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

Dear Ms. Ramos:

Please refer to your Supplemental New Drug Application (sNDA) dated September 29, 2010, 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 October 5, December 14, 2010, and September 30, 2011.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows:

1. In HIGHLIGHTS/DRUG INTERACTIONS, the bullet on statins has been changed from:

   Statins: Follow label recommendations for concomitant use of certain statins with a CYP 3A and P-gP inhibitor like dronedarone (7.3)

   To:

   Statins: Avoid simvastatin doses greater than 10 mg daily. Follow label recommendations for concomitant use of other statins with a CYP 3A and P-gp inhibitor like dronedarone (7.3)

2. Section 7 (DRUG INTERACTIONS) has been substantially revised and now reads as follows:

   7 DRUG INTERACTIONS

   7.1 Pharmacodynamic Interactions

   Drugs prolonging the QT interval (inducing Torsade de Pointes)
   Co-administration of drugs prolonging the QT interval (such as certain phenothiazines, tricyclic antidepressants, certain macrolide antibiotics, and Class I and III antiarrhythmics) is contraindicated because of the potential risk of Torsade de Pointes-type ventricular tachycardia *[see Contraindications (4), Clinical Pharmacology (12.3)]*.

   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.

Calcium channel blockers
Calcium channel blockers with depressant effects on the sinus and AV nodes could potentiate dronedarone's effects on conduction.
Give a low dose of calcium channel blockers initially and increase only after ECG verification of good tolerability *[see Drug Interactions (7.3)]*.

Beta-blockers
In clinical trials, bradycardia was more frequently observed when dronedarone was given in combination with beta-blockers.
Give a low dose of beta-blockers initially, and increase only after ECG verification of good tolerability *[see Drug Interactions (7.3)]*.

7.2 Effects of Other Drugs on Dronedarone

Ketoconazole and other potent CYP 3A inhibitors
Concomitant use of ketoconazole as well as other potent CYP 3A inhibitors such as itraconazole, voriconazole, ritonavir, clarithromycin, and nefazodone is contraindicated because exposure to dronedarone is significantly increased *[see Contraindications (4), Clinical Pharmacology (12.3)]*.

Grapefruit juice
Patients should avoid grapefruit juice beverages while taking MULTAQ because exposure to dronedarone is significantly increased *[see Clinical Pharmacology (12.3)]*.

Rifampin and other CYP 3A inducers
Avoid rifampin or other CYP 3A inducers such as phenobarbital, carbamazepine, phenytoin, and St John's wort because they decrease exposure to dronedarone significantly *[see Clinical Pharmacology (12.3)]*.

Calcium channel blockers
Verapamil and diltiazem are moderate CYP 3A inhibitors and increase dronedarone exposure. Give a low dose of calcium channel blockers initially and increase only after ECG verification of good tolerability *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

7.3 Effects of Dronedarone on Other Drugs

Simvastatin
Dronedarone increased simvastatin/simvastatin acid exposure. Avoid doses greater than 10 mg once daily of simvastatin *[see Clinical Pharmacology (12.3)]*.

Other statins
Because of multiple mechanisms of interaction with statins (CYPs and transporters), follow statin label recommendations for use with CYP 3A and P-gp inhibitors such as dronedarone.

Calcium channel blockers
Dronedarone increased the exposure of calcium channel blockers (verapamil, diltiazem or nifedipine). Give a low dose of calcium channel blockers initially and increase only after ECG verification of good tolerability *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Sirolimus, tacrolimus, and other CYP3A substrates with narrow therapeutic range
Dronedarone can increase plasma concentrations of tacrolimus, sirolimus, and other CYP 3A substrates with a narrow therapeutic range when given orally. Monitor plasma concentrations and adjust dosage appropriately.

Beta-blockers and other CYP 2D6 substrates
Dronedarone increased the exposure of propranolol and metoprolol. Give low doses of beta-blockers initially, and increase only after ECG verification of good tolerability. Other CYP 2D6 substrates, including other beta-blockers, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) may have increased exposure upon co-administration with dronedarone *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

P-glycoprotein substrates
Digoxin
Dronedarone increased digoxin exposure by inhibiting the P-gp transporter. Reconsider the need for digoxin therapy. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Dabigatran
Exposure to dabigatran is higher when it is administered with dronedarone than when it is administered alone.

Other P-gp substrates are expected to have increased exposure when co-administered with dronedarone.

Warfarin
When co-administered with dronedarone exposure to S-warfarin was slightly higher than when warfarin was administered alone. There were no clinically significant increases in INR *[see Clinical Pharmacology (12.3)]*. More patients experienced clinically significant INR elevations (≥ 5) usually within 1 week after starting dronedarone vs. placebo in patients taking oral anticoagulants in ATHENA. However, no excess risk of bleeding was observed in the dronedarone group.
Postmarketing cases of increased INR with or without bleeding events have been reported in warfarin-treated patients initiated on dronedarone. Monitor INR after initiating dronedarone in patients taking warfarin.

3. Under section 12.3 Pharmacokinetics, the following has been added as a new Drug Interactions subsection:

Drug Interactions
Dronedarone is metabolized primarily by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6. Dronedarone has no significant potential to inhibit CYP 1A2, CYP 2C9, CYP 2C19, CYP 2C8 and CYP 2B6. It has the potential to inhibit P-glycoprotein (P-gp) transport. Dronedarone inhibits *in vivo* the tubular secretion of creatinine a substrate of the organic cation transporter (OCT2) *[see Warnings and Precautions (5.8)]*. *In vitro* studies demonstrate that dronedarone or its metabolites are weak inhibitors of organic cation transporter (OCT1), organic anion transporting polypeptide (OATP1B1, OATP1B3), and organic anion transporter (OAT3). Monamine oxidases contribute partially to the metabolism of the active metabolite of dronedarone.

Pharmacokinetic measures indicating the magnitude of these interactions are presented in Figure 1 (impact of co-administered drugs on dronedarone) and Figure 2 (impact of dronedarone on co-administered drugs).

Figure 1: The impact of co-administered drugs on the pharmacokinetics of dronedarone and recommendations for dronedarone coadministration or dose adjustment.

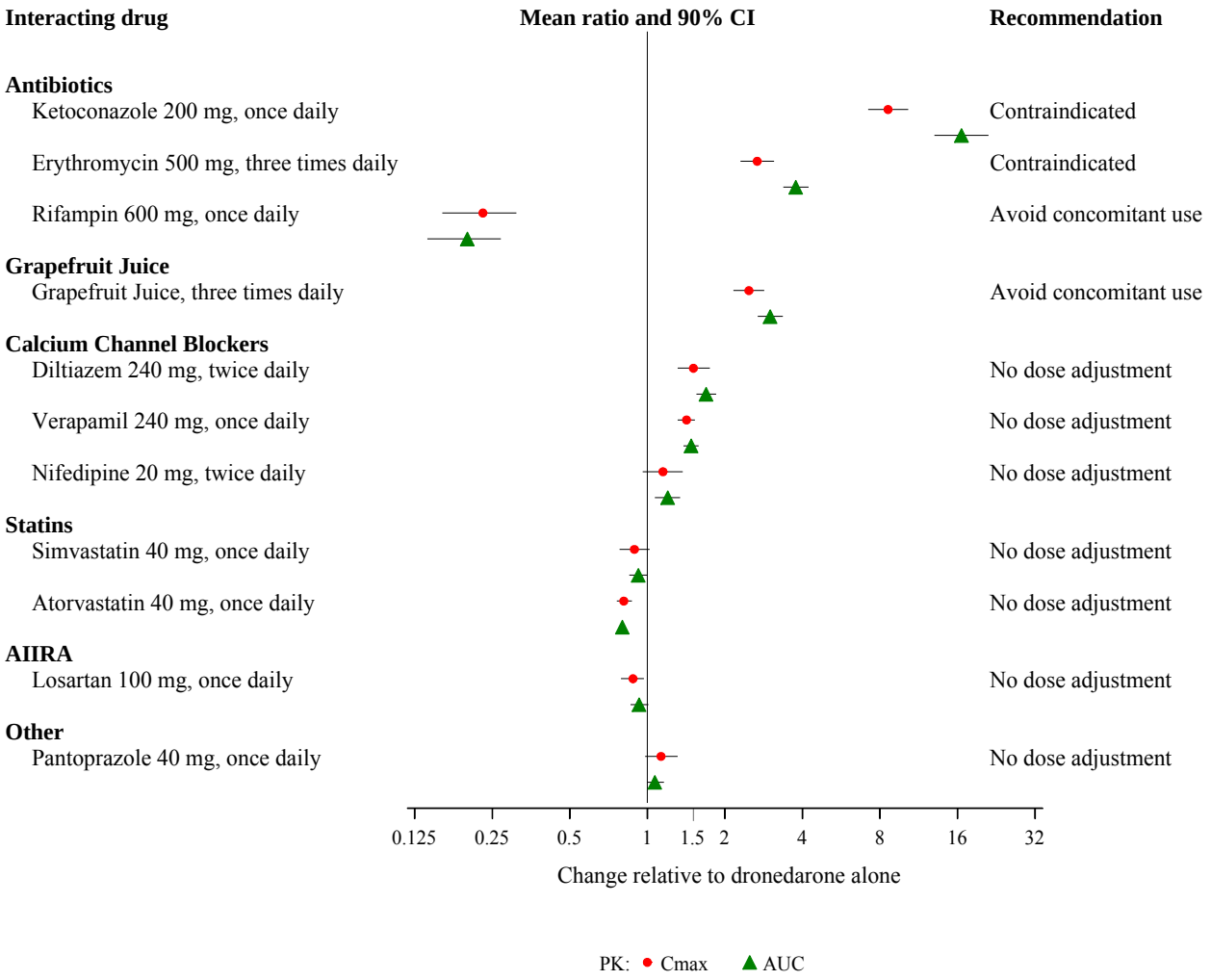
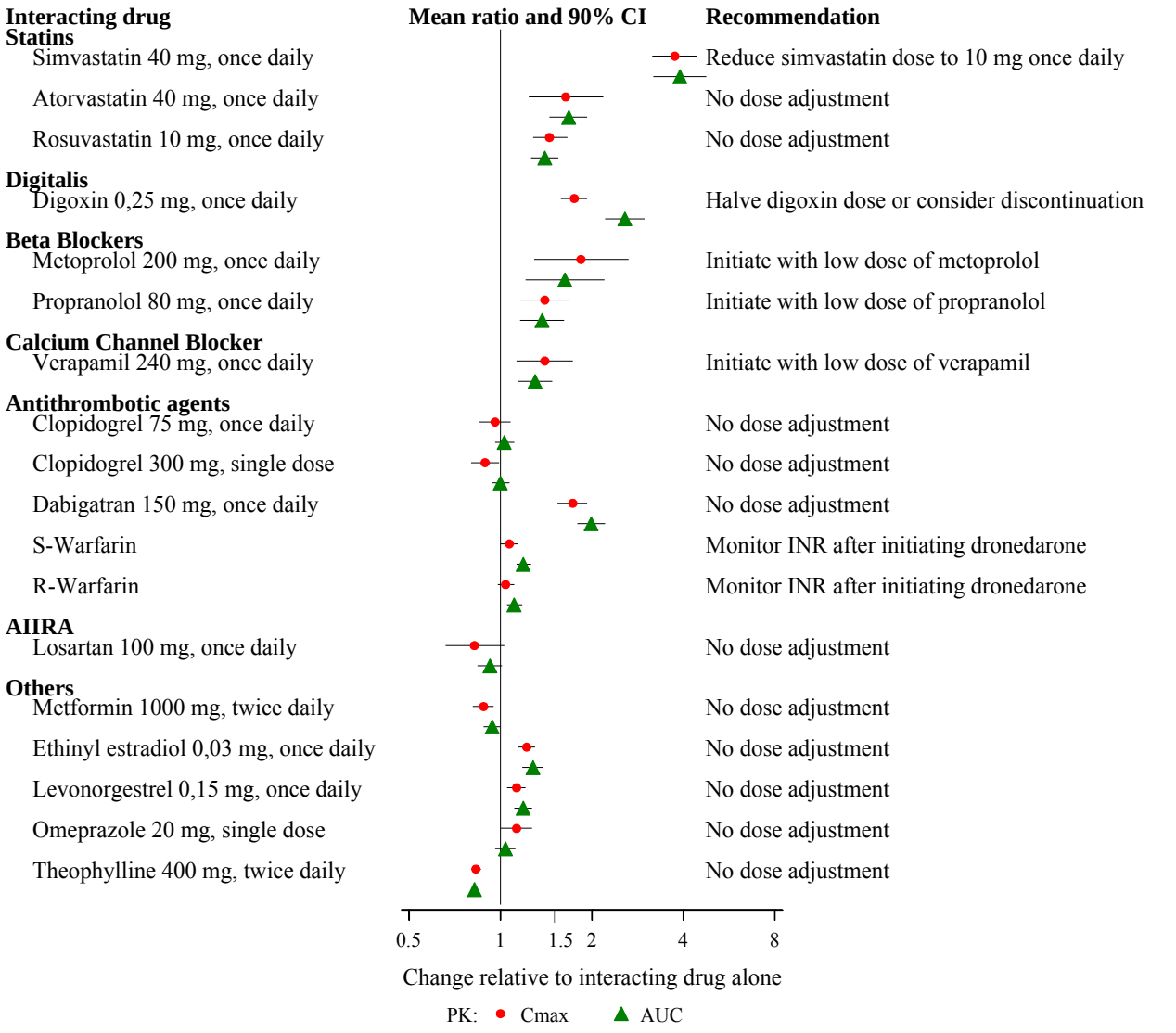


Figure 2: The impact of dronedarone on co-administered drugs and recommendations for dose adjustment of co-administered drug.



We have completed our review of this supplemental 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, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any 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.

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to 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, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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

Enclosure: Content of Labeling

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
01/25/2012