

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-425**

**RISK ASSESSMENT and RISK  
MITIGATION REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 8, 2009

To: Norman Stockbridge, M.D., Director  
Division of Cardiovascular and Renal Products (DCRP)

Thru: Claudia Karwoski, Pharm. D., Director (acting)  
Division of Risk Management (DRISK)

From: Elizabeth Donohoe, M.D., Risk Management Analyst, DRISK  
Kate Heinrich, M.A., Health Education Reviewer, DRISK  
Allen Brinker, M.D., MPH, Epidemiology Team Leader, Division  
of Epidemiology

Subject: Review of proposed Risk Evaluation and Mitigation Strategy  
(REMS)

Drug Name(s): Dronedarone [Multaq]

Application Type/Number: NDA 022425

Applicant/sponsor: Sanofi-Aventis

OSE RCM #: 2009-1374

## 1 INTRODUCTION

The sponsor submitted a revised proposed Risk Evaluation and Mitigation Strategy (REMS) for dronedarone [NDA 022425] based upon the Agency's review of earlier versions of the proposed REMS. Please see Appendix 1, Preliminary Review with track changes forwarded to DCRP on May 21, 2009 for DRISK comments based on materials submitted prior to that date.

Dronedarone, trade name Multaq, has a proposed indication 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 who are in sinus rhythm or will be cardioverted. The sponsor's submission is in response to informal requests and comments provided by the review division prior to and following the Cardiovascular and Renal Drugs Advisory Committee meeting held March 18, 2009.

DCRP requested a consult by DRISK to review the revised proposal. This review is based on materials listed below.

## 2 MATERIAL REVIEWED

- Proposed REMS submitted June 4, 2009 [version 6.0, dated June 3, 2009]; and
- REMS Supporting Documents [version 5.0, dated June 3, 2009].

## 3 BACKGROUND

The Sponsor originally submitted a Risk Minimization Action Plan (RiskMAP) with the NDA on July 31, 2008. The RiskMAP appears to have been submitted voluntarily by Sponsor since the not approvable letter, dated August 29, 2006, did not indicate a need for the sponsor to submit a RiskMAP. The Sponsor subsequently submitted a REMS on January 22, 2009 and presented their proposal to the Advisory Committee Meeting on March 18, 2009.

The revised REMS proposal was submitted following the AC based upon feedback provided by OSE and DCRP, including a comment to focus the REMS on the potential risk of worsening heart failure. Based on communication from DCRP to the sponsor after a face to face meeting on May 15, 2009, the sponsor was officially informed of the requirement to submit a REMS. This review addresses the sponsor's response to DRISK's prior comments [see Appendix 1].

## SPONSOR'S PROPOSED REMS

### 1. Proposed REMS:

In brief, the proposed REMS for Multaq [version 6.0] is satisfactory with the exception of the comment below:

The sponsor's REMS resubmission (version 6.0), section B. Communication Plan 1a., includes the wording: (b) (4)

DRISK recommends rewording this section to state:

Sanofi-aventis will distribute the *Healthcare Professional Information Sheet* through hardcopy mailings by U.S. mail. In addition, this information will be made available through electronic communication and on the product website.

### 2. Supporting Document:

DRISK has three comments related to information provided in the Supporting Document (version 5.0):

a. The "Supporting Documents" of the sponsor's prior submission (version 4.0) includes the information below; this was removed from the resubmission (Version 5.0)

### 3.2.1 Targeted Groups

(b) (4)



If the above information is still accurate, this language needs to be added back into the Supporting Document. Otherwise, the sponsor needs to include information about how stakeholders will be targeted in the Supporting Documents.

b. The sponsor did not address DRISK's comment #3b (Please see Appendix 1):

The key stakeholders are appropriate; please clarify in the REMS how the secondary stakeholders will be targeted.

This clarification should be included in the Supporting Document.

c. The "Supporting Documents" of the sponsor's prior submission (version 4.0) indicated that the "distribution" to targeted stakeholders would include Information Sheet, Prescribing Information and Medication Guide. The resubmission version 5.0 does not include this information. The sponsor's "REMS" only states that the Information Sheet will be distributed yet wording in the Information Sheet states: "Please refer to the enclosed Prescribing Information". The sponsor needs to clarify exactly what materials will be included in the distribution to stakeholders.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

In its proposed REMS resubmission on June 4, 2009, the sponsor has generally met the requirements for an acceptable REMS submission. The proposed REMS and REMS Supporting Document should be resubmitted based upon the comments below, pending DCRP review.

Comments for the Sponsor:

1. Regarding the REMS (version 6.0) – Revise as follows:

REMS section B. Communication Plan 1a.:

Sanofi-aventis will distribute the *Healthcare Professional Information Sheet* through hardcopy mailings by U.S. mail. In addition, this information will be made available through electronic communication and on the product website.

2. Regarding the REMS Supporting Documents (version 5.0) – Revise as follows:

a. The "Supporting Documents" of your prior submission (version 4.0) includes the information below; this was removed from the resubmission (version 5.0).

### 3.2.1 Targeted Groups

(b) (4)



If the above information is still accurate, add this language back into the Supporting Document. Otherwise, you need to include information about how stakeholders will be targeted in the Supporting Documents.

b. Clarify in the Supporting Document how the secondary stakeholders will be targeted.

c. The "Supporting Documents" of your prior submission (version 4.0) indicated that the "distribution" to targeted stakeholders would include Information Sheet, Prescribing Information and Medication Guide. The resubmission version 5.0 does not include this information. Your "REMS" only states that the Information Sheet will be distributed yet wording in the Information Sheet states: "Please refer to the enclosed Prescribing Information". You need to clarify exactly what materials will be included in the distribution to stakeholders.

3. Submit the REMS, Supporting Document, and appended materials in "Word" as well as "Adobe" formats. The Word versions should be submitted as "track changes" and a "clean" copy.

**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of New Drugs 1  
Division of Cardiovascular and Renal Products**

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**NDA/BLA #s:** NDA 22-425  
**Products:** MULTAQ (dronedarone HCl) Tablets, 400 mg  
**SPONSOR:** sanofi-aventis  
**FROM:** Robert Temple, M.D.  
**DATE:** April 30, 2009

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Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a 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)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for dronedarone to ensure that the benefits of the drug outweigh the risk of fatal outcomes in patients taking Multaq (dronedarone) who have New York Heart Association (NYHA) Class IV heart failure or NYHA Class II and III heart failure and a recent hospitalization or referral to a specialized heart failure clinic for decompensated heart failure. In reaching this determination, we considered the following:

- A. The estimated number of patients in the United States with atrial fibrillation (AF) is nearly 3 million and expected to increase to close to 5.6 million by 2050.<sup>1</sup> This year,

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<sup>1</sup> Go, "Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention." *JAMA*, 2001;285:2370-2375.

**REMS memo Dronedarone**

there will be over 200,000 new cases. Americans over 40 years of age have a 1 in 4 lifetime risk of developing AF.<sup>2</sup>

- B. Patients with AF have an increased risk of hospitalization for heart-related events.
- C. Multaq (dronedarone) has been shown to be effective in reducing the risk of cardiovascular hospitalization in patients with AF.
- D. Multaq (dronedarone) is indicated in patients with a history of paroxysmal or persistent atrial fibrillation. The drug may be used chronically.
- E. Multaq (dronedarone) is contraindicated in patients with New York Heart Association (NYHA) Class IV heart failure and NYHA Class II and III heart failure who have had a recent hospitalization or referral to a specialized heart failure clinic for decompensated heart failure. In a large study, patients with these characteristics demonstrated an increase in fatal outcomes with Multaq (dronedarone) therapy. Other adverse events associated with Multaq (dronedarone) use include: gastrointestinal disorders, QT prolongation, rash, and increased creatinine.
- F. Dronedarone is a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that dronedarone poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of dronedarone. FDA has also determined that dronedarone is a product for which patient labeling could help prevent serious adverse events.

The elements of the REMS will be a Medication Guide, Communication Plan and a timetable for submission of assessments of the REMS.

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<sup>2</sup> <sup>82</sup>Van Wagoner, David "Atrial selective strategies for treating atrial fibrillation." *Drug Discovery Today: Therapeutic Strategies* Vol 2, No. 3, 2005. "We have detected increased levels of the systemic inflammatory marker C-reactive protein (CRP) in patients with A-Fib."

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/s/

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5/15/2009 03:49:40 PM  
CSO

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MEDICAL OFFICER