CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-425

OTHER REVIEW(S)

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Maternal Health Team Label Review

Date: May 8, 2009 **Date Consulted:** April 27, 2009

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Cardio-renal Products

Drug: Multaq (dronedarone) NDA 22 425

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Multaq labeling

Consult Question: Please review sections of the proposed label as they relate to pregnancy and lactation.

INTRODUCTION

On June 27, 2008, Sanofi-Aventis submitted a new drug application (NDA) to the Division of Cardio-renal products for Multaq (dronedarone). Multaq is an antiarrythmic agent; the

sponsor's proposed indication is for 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, to reduce the risk of cardiovascular hospitalization.

On April 27, 2008, the Division of Cardio-renal products requested that the Maternal Health Team (MHT) review the pregnancy and nursing mothers section of the Multaq package insert, and provide comment. This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of Multaq labeling.

BACKGROUND

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of Multaq labeling.

SUMBMITTED MATERIAL
Sponsor's Proposed Pregnancy and Nursing Mothers Labeling

4 CONTRAINDICATIONS

- Pregnancy (Category X): MULTAQ may cause fetal harm when administered to a pregnant woman. (b) (4)

  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)*] and
- Lactation [*see Use in specific populations (8.3)*].

8.1 Pregnancy

Pregnancy Category X [*see Contraindications (4)*]
(b) (4)

(b) (4) 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 the fetus.

MULTAQ was teratogenic in rats given oral doses ≥80 mg/kg/day [a dose equivalent to the maximum recommended human dose (MHRD) on a mg/m^2 basis)], with fetuses showing external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactylia, syndactylia, and anterior and/or posterior club feet). In rabbits, dronedarone caused an increase in skeletal abnormalities (anomalous ribcage and vertebrae, pelvic asymmetry) at doses ≥20 mg/kg (the lowest dose tested and approximately half the MRHD on a mg/m^2 basis).

(b) (4)

8.3 Nursing Mothers

Dronedarone and its metabolites are excreted in rat milk. Nursing in lactating rats administered dronedarone was associated with minor reduced body-weight gain in the offspring. It is not known whether this drug is excreted in human milk. (b) (4) [*see Contraindications (4)*].

DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule was published May 2008. While the final rule is being written and cleared, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians. MHT has created a new section under Warnings to advise women of reproductive age regarding the need for contraception while using Multaq to prevent inadvertent fetal exposure.

The MHT's recommended labeling for Multaq is provided on pages 4-5 of this review.

RECOMMENDATIONS

Provided below are the MHT's recommended revisions to the sponsor's proposed labeling.

Highlights of Prescribing Information:

CONTRAINDICATIONS

- Pregnancy (4, 8.1)
- Nursing Mothers (4, 8.3)

WARNINGS AND PRECAUTIONS

- Women of childbearing potential should use effective contraception while using MULTAQ (5.6)

4. CONTRAINDICATIONS

- 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)*].

WARNINGS

5.6 Women of Childbearing Potential

Premenopausal women who have not undergone a hysterectomy and/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)*].

8.1 Pregnancy

Pregnancy Category X [*see Contraindications (4)*]

MULTAQ may cause fetal harm when administered to a pregnant woman. In animal studies, MULTAQ was teratogenic in rats at the maximum recommended human dose (MRHD), and in rabbits at half the MRHD. 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 the fetus.

When pregnant rats received dronedarone at oral doses greater than or equal to the MRHD (on a mg/m^2 basis), fetuses had increased rates of external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactylia, syndactylia, and anterior and/or posterior club feet). When pregnant rabbits received dronedarone, at a dose approximately half the MRHD (on a mg/m^2 basis), fetuses had an increased rate of skeletal abnormalities (anomalous ribcage and vertebrae, pelvic asymmetry).

Actual animal doses: rat ($\geq$80 mg/kg/day); rabbit ($\geq$20 mg/kg)

8.2 Labor and Delivery

It is not known whether dronedarone affects labor or delivery in humans. In pre- and post-natal development studies in the rat, at doses up to 2/3 the MRHD, dronedarone induced no effect on the duration of gestation or on parturition.

8.3 Nursing Mothers

It is not known whether MULTAQ is excreted in human milk. Dronedarone and its metabolites are excreted in rat milk. During a pre- and post-natal study in rats, maternal dronedarone administration was associated with minor reduced body-weight gain in the offspring. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MULTAQ, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother [*see Contraindications (4)*].

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/s/

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5/11/2009 02:53:53 PM
MEDICAL OFFICER

Karen Feibus
5/11/2009 03:58:35 PM
MEDICAL OFFICER
I agree with the content and recommendations contained in this review

Lisa Mathis
5/12/2009 09:04:19 AM
MEDICAL OFFICER

MEMORANDUM

To: **Russell Fortney**
Division of Cardiovascular and Renal Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **April 28, 2009**

Re: **Comments on draft labeling for Multaq (dronedarone) tablets**
NDA 22-425

We have reviewed the proposed label for Multaq (FDA version dated 4/22/09) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

Please see attached label for recommended changes.

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X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Other Reviews 1

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/s/

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DDMAC PROFESSIONAL REVIEWER

Laurie Burke
6/2/2009 11:26:14 PM
INTERDISCIPLINARY

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:	May 8, 2009
To:	**Norman Stockbridge, MD, PhD, Director** Division of Cardiovascular and Renal Products (DCRP)
Through:	Claudia Karwoski, PharmD, Director (Acting) **Division of Risk Management** Jodi Duckhorn, MA, Team Leader **Division of Risk Management**
From:	Nancy Carothers RN, BA Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling
Drug Name(s):	MULTAQ™ (dronedarone) Tablets
Application Type/Number:	NDA 22-425
Applicant/sponsor:	Sanofi Winthrop Industrie
OSE RCM #:	2008-1374

1 INTRODUCTION

Multaq (dronedarone) is an antiarrhythmic drug that was initially developed with the intent of (b) (4) . The proposed indication is for patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with associated cardiovascular risk factors and a recent episode of AF/AFL, who are in sinus rhythm or who will be cardioverted, to reduce the risk of cardiovascular hospitalization.

The Agency informed the Applicant that dronedarone would require a Risk Evaluation and Mitigation Strategy (REMS) 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.

The Applicant initially proposed a REMS that included a Medication Guide but was subsequently instructed by the Division of Cardiovascular and Renal Products (DCRP) that a MG was not necessary. The Applicant subsequently submitted a proposed patient package insert (PPI) for dronedarone.

The proposed REMS also includes a communication plan, a timetable for submission of assessments, and an assessment plan. These elements are being reviewed separately and will be addressed in a separate DRISK review.

2 MATERIAL REVIEWED

- Proposed MULTAQ™ (dronedarone) tablets Patient Package Insert (PPI), received from the Review Division with their revisions on April 19, 2009.
- Proposed MULTAQ™ (dronedarone) tablets Prescribing Information (PI), received from the Review Division with their revisions on April 19, 2009.

3 DISCUSSION

DCRP informed sanofi aventis that a MG was not a necessary element of the REMS because there is no clear evidence that dronedarone worsens heart failure (HF) as the clinical trial only indicated a higher rate of mortality in patients with more severe HF. They also explained to DRISK that patients with HF are likely to be counseled by their providers and/or are likely to seek medical treatment if HF worsens irrespective of treatment with dronedarone, thus a MG is not needed to tell them to do so.

While there may not be clear evidence that dronedarone worsens heart failure, the proposed label contraindicates its use in certain patients with severe heart failure and includes a warning that patients should be advised by their provider to consult a physician if they develop signs or symptoms of heart failure. While this type of counseling might already occur in clinical practice, information provided in a MG may serve to reinforce the message. The Center has taken similar measures with other drugs that have been associated with heart failure. The thiazolidinediones have been associated with new or worsening heart failure and a MG was utilized to convey this information and to advise patients to call their doctor if they develop signs and symptoms of heart failure.

Furthermore, we believe that a Medication Guide is necessary for patients' safe and effective use of dronedarone and it meets at least 1 of the 3 circumstances required under 21 CFR 208.1: the drug product is one for which patient labeling could help prevent serious adverse events. There are a few circumstances in which one may consider not requiring a MG for a drug that meets any of the 3 criteria under 208. One circumstance might be if the information is so complex or cannot be easily conveyed to the intended population. For example, DRISK recommend against the use of a MG for the antipsychotic drugs to convey the risk of increased mortality in patients treated for dementia-related psychosis: there is no clear message to convey to patients or caregivers or specific instructions as to how patients should be monitored or what families or other caregivers can look for; there is no explicit labeling statement recommending against use in this population; there are no known risk factors to identify patients who should not be receiving this therapy, nor are there any known criteria to select patients with a more favorable risk-benefit ratio. DRISK also recommend against a MG for Entereg, a drug that is used only in an inpatient setting for short term use, while the cardiac risk is associated with long term use. Neither of these circumstances exists with dronedarone.

Sanofi aventis initially proposed a MG because they felt the information necessary for patients and the MG would reinforce the patient counseling information provided by the prescriber. We agree with the company that patient labeling could help reinforce messages and at worst provides redundant information. At best, the MG provides information that a busy HCP did not have time to discuss with patients. While the communication plan is a key element of the REMS, it is unlikely that all prescribers will receive the communication plan materials and that consistent counseling messages will be conveyed to patients. With the exception of the Entereg REMS, FDA has not approved a REMS that has a communication plan for prescribers without some risk communication to patients. A MG provides another mechanism to patients with consistent messages about the safe use of the drug.

After further internal discussion, the DCRP agreed with a Medication Guide for dronedarone. The formal REMS notification letter is currently being drafted.

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the Applicant has a Flesch Kinkaid grade level of 7.9, and a Flesch Reading Ease score of 61.1%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The revised MG has a Flesch Kinkaid grade level of 5.9 and a Flesch Reading Ease score of 72.4%.

In our review of the PPI we have:

- reformatted the PPI to make consistent with MG,
- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).
- Finally we renamed the PPI a MG following discussion with the DCRP

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS

We recommend patient labeling in the form of a Medication Guide as discussed above. This was submitted by the applicant as a Patient Package Insert. Our modifications include a number of editorial changes as well as changes in the question and answer format to follow the requirements of the information that must be included in a Medication Guide. These changes to the Applicant's proposed patient labeling potentially enhance the safe use of this product, and are indicated in the DRISK Comments in the review and in the Conclusions and Recommendations that follow.

These modifications reflect labeling that was sent to DRISK on April 19, 2009. Any additional changes to the PI would also need to be reflected in the MG.

In the section, "What is the most important information I should know about MULTAQ?"

- patients are warned that people with severe heart failure should not take MULTAQ. They are told to tell their doctor if they have experienced even one episode of shortness of breath or leg swelling. We did not delete "leg swelling" even though this sign does not appear in the PI under Contraindications or in the boxed warning, because "dependent edema" is in the Warnings and Precautions" section of the PI (5.1). We recommend the inclusion of this sign of impending heart failure.

- patients are instructed to call their doctor right away if they have any signs and symptoms of heart failure. These are listed here because MULTAQ is contraindicated in patients with heart failure. See 14.3. We suggest that the phrase "coughing that does not stop" be added to the phrase "coughing up frothy **(b) (4)** sputum" so that patients are calling their doctor as early as possible in this process.

- there are two lists of medicines. The first list includes medicines that are contraindicated when taking MULTAQ and the second list has medicines that patients should tell their doctor about. Both lists have been moved to more appropriate sections of the MG. The first list is under, "Who should not take MULTAQ" because these drugs are in the Contraindications section of the PI. The second list is under "Tell your doctor about all the medicines you take" because these drugs are not contraindicated.

In the section, "Who should not take MULTAQ?"

- The list of medicines that patients should not take when using MULTAQ is located under the subheading in this section "Do no (b) (4) MULTAQ:" All of these medicines are included in the Contraindications section of the PI. However, we added "Voriconazole" because it was not in the MG but was in the Contraindications section of the PI.

- We added "Medicines for bacterial infection" in the last bullet under the subheading "Some medicines that can affect how quickly your heart beats:" because the PI includes "certain oral macrolide antibiotics" in the Contraindications section under this category of drugs that may prolong QT intervals. Since we are using 'conditions" in this section, we added the condition "bacterial infection." The drug names that appear in this section of the MG have been deleted because the PI lists only classes of drugs for specific conditions, without drug names. The MG must be consistent with the PI. We recommend, when possible, not listing single drug names but classes of drugs (if all drugs in the class are included) or conditions. If individual drug names are listed, the applicant must ensure that all of the brand and generic names of the drugs in each class are included because patients may think their drug is "safe" if it is not listed here.

In the section, "What should I tell my doctor before starting MULTAQ?"

There are (b) bullets in this section describing health conditions that patients should tell their doctor about. These are (b) (4)
(b) (4), and these have been deleted because these conditions are included as "Contraindications" in the PI. These appear in the section, "Who should not take MULTAQ."

In the section, "Tell your doctor about all the medicines you take."

The PI says that the medicines listed under this heading (and the subtitle, "Be sure to tell your doctor and pharmacist if you take") should not be taken with MULTAQ because they decrease exposure to the drug 5-fold. See 7.2. However, these medicines are not listed under Contraindications. We defer to the Review Division as to whether "should not be taken with" means that these medicines are "contraindicated" and should be under the "Who should not take MULTAQ?" section of the MG. In addition, we deleted all of the drug names used in this section because we recommend, when possible, not listing individual drug names but classes of drugs (if all drugs in the class are included) or conditions for which drugs are taken. The drug names used here are not in the PI. If individual drug names are listed, the applicant should ensure that all of the brand and generic names of the drugs are included because patients may think their drug is "safe" if it is not listed.

In the section, "How should I take MULTAQ?"

- In the second bullet in this section we recommend not including the actual dosage since dosages may change. We defer to the Review Division as to whether the dose of "one tablet" or "400 mg." should be included in the MG in order to enhance the safe use of this product.

- We have instructed patients, in the 6th bullet, in this section to always remain under the care of their doctor while taking MULTAQ because the Patient Counseling section of the PI offers this advice. This makes a stronger statement when added to the original one which says to (b) (4)

In the section, "What are the possible side effects of MULTAQ?"

- We added a section, "What are the (b) (4) side effects of MULTAQ?" because of the boxed warning and contraindications that describe the dangers of "worsening heart failure" in patients taking MULTAQ. In addition, we added "bradycardia" because it appears on Table 1 of the Adverse Drug Reactions and occurred in 3% of patients studied. We consider worsening heart failure and bradycardia to be "serious side effects."
- In the section, "What are the most (b) (4) side effects?" we deleted any "(b) (4)" side effects that occurred in less than 3% of patients. All of the side effects listed occurred in 3% or more of patients studied. See Table 1 under Adverse Reactions (6).
- We added the following statement to the end of the section, "What are the possible side effects of MULTAQ?":

  Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

  This verbatim statement is required for all Medication Guides. [1]

In the section, "How should I store MULTAQ?"

- The patient is instructed to store MULTAQ at room temperature (b) (4) It would be extremely difficult for patients to keep their medicine at exactly (b) (4). It would be more appropriate to list a temperature range, but a range is not provided in the PI. If a range is added to the PI, it may also be changed in this MG.

- The instructions in the MG, to keep MULTAQ in its original packaging and to discard where children can not get the tablets, are not in the PI and must be added to the PI to be used in the MG. The MG must be consistent with the PI. We recommend adding this information to the PI and MG to increase safe use of this product.

Please let us know if you have any questions.

[1] 21 CFR 208.20 (b)(7)(iii)

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X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Other Reviews 2

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/s/

Mary Dempsey
5/13/2009 07:36:50 AM
DRUG SAFETY OFFICE REVIEWER

Mary Dempsey
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Claudia Karwoski
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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:	January 6, 2009
To:	Norman Stockbridge, MD, Director Division of Cardiovascular and Renal Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Jinhee J. Lee, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Multaq (Dronedarone HCl) Tablets 400 mg
Application Type/Number:	NDA # 22-425
Applicant/Applicant:	Sanofi-Aventis U.S. Inc.
OSE RCM #:	2008-1373

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EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis (DMEPA) noted areas of needed improvement for the container labels, carton and insert labeling of Multaq. Improvements include the prominence, presentation, and consistency of information that is vital to the safe use of the product. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Cardiovascular and Renal Products to review the Applicant's container labels carton and insert labeling. DMEPA reviewed the Applicant's proposed container labels, carton and insert labeling submitted on June 27, 2008.

1.2 REGULATORY HISTORY

DMEPA previously reviewed the name, Multaq, without objection in ODS Consult # 05-0075-1, Proprietary Name Review for Multaq (NDA 21-913) dated January 30, 2006. In that consult, we also provided label and labeling recommendations which were subsequently forwarded to the Applicant.

1.3 PRODUCT INFORMATION

Multaq is the proposed name for Dronedarone tablets. Dronedarone is an antiarrhythmic drug proposed to be indicated in patients with a history of, or current atrial fibrillation or atrial flutter, for the reduction of the risk of cardiovascular hospitalization or death.

The recommended starting dosage is 400 mg twice daily. Multaq should be taken as one tablet with the morning meal and one tablet with the evening meal.

Treatment with class I or (b) antiarrhythmics (such as flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol, amiodarone) must be stopped before starting Multaq.

Treatment with Multaq can be initiated in an outpatient setting.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA conducting a label, labeling, and/or packaging risk assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because the DMEPA staff analyzes reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMEPA uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

DMEPA reviewed the following labels and labeling submitted by the Applicant on June 27, 2008. See Appendices A through C for pictures of the labels and labeling.

- Container Labels (60 tablet, 180 tablet, and 500 tablet)
- Blister Label
- Blister Carton Labeling
- Package Insert Labeling (no image)
- Patient Package Insert/Medication Guide (no image)

3 RESULTS

3.1 GENERAL COMMENTS

The established name does not have prominence commensurate with the proprietary name.

The strength is expressed as the base, however, the established name is expressed as the salt.

3.2 CONTAINER LABELS

The dosage form statement, tablet, has been omitted from the labels and labeling.

The drug product is packaged in a "unit of use" bottle containing 60 tablet (for 30 days) and 180 tablets (for 90 days).

3.3 BLISTER LABELS

The dosage form statement appears immediately after the strength statement instead of in conjunction with the established name.

3.4 BLISTER CARTON LABELING

See General Comments.

The net quantity statement appears as "(b) (4)

3.5 PACKAGE INSERT LABELING

The established name appears as "Dronedarone" and the dosage form as "film-coated tablets". This presentation is different than what is on the container/blister labels and carton labeling.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3.6 PATIENT PACKAGE INSERT/MEDICATION GUIDE

No comments from a medication error perspective.

4 DISCUSSION

4.1 PROMINENCE OF ESTABLISHED NAME

Although the font size of the established name appears ½ the size of the proprietary name, it does not have a prominence commensurate with the prominence of the proprietary name. It does not take into account all pertinent factors, including typography, layout, contrast, and other printing features. The disparity in size may be attributed to the outlining of the proprietary name which increases the prominence of the name. Thus, this presentation is not in accordance with 21 CFR 201.10(g)(2).

4.2 EXPRESSION OF ESTABLISHED NAME AND DOSAGE FORM ON CONTAINER/BLISTER LABELS, BLISTER CARTON AND PACKAGE INSERT LABELING

The strength of this product is expressed based on the active moiety Dronedarone and not the salt Dronedarone Hydrochloride. Thus, the established name should be expressed as 'Dronedarone' and not 'Dronedarone HCl' to match the dosage form strength. These comments are consistent with recommendations provided in the Chemistry information request letter to the Applicant dated July 3, 2008.

Furthermore, the dosage form appears as "film-coated tablets" on the insert labeling. However, this presentation is different than what is on the container/blister labels and blister carton labeling. DMEPA defers to ONDQA to evaluate the appropriateness of the "film-coated" descriptor and designation of the established name.

Additionally, per our e-mail communication with the assigned Chemist from Office of New Drug Quality Assessment (ONDQA) on November 14, 2008, the established name, dosage form, and strength should appear as follows:

Multaq (Dronedarone) Tablets 400 mg

4.3 CHILD RESISTANT CLOSURE

It is unclear whether the 60 and 180 tablet bottles have a Child Resistant Closure (CRC). Since 60 and 180 tablet bottles provide a one month and 3 month supply, respectively, these sizes can be considered unit-of-use bottles based on the dosing of this product. Therefore, ensure that the cap is CRC to be in accordance with the Poison Prevention Packaging Act of 1970.

4.4 BLISTER CARTON LABELING

The blister carton labeling includes a (b) (4) The presentation of this statement does not clearly convey the contents of the carton because it includes the abbreviation, (b) (4) It would be preferable and in alignment with conventional label/labeling layout if the statement instead was presented as "10 x 10 unit dose blisters".

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, DMEPA notes problems with the prominence, presentation, and consistency of information that is vital to the safe use of the product. DMEPA believes the risks we have identified can be addressed and mitigated prior to

drug approval, and provides recommendations in Section 5.1 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

Although we observed some improvements that could be made to the Patient Package Insert/Medication Guide, we provided the Division of Risk Management with our comments which will be incorporated into their forthcoming review (OSE Review #2008-1374). We defer any remaining comments regarding the patient package insert/medication guide to the Division of Risk Management.

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, OSE project manager, at 301-796-1332.

5.2 COMMENTS TO THE APPLICANT

Based upon our assessment of the labels and labeling, DMEPA identified the following areas of needed improvement.

A. All Labels and Labeling

1. Although the font size of the established name appears ½ the size of the proprietary name, it does not have a prominence commensurate with the prominence of the proprietary name. It does not take into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the labels and labeling to increase the prominence of the established name in accordance with 21 CFR 201.10(g)(2).
2. Revise the established name, dosage form, and strength so that it appears as follows:

   Multaq (Dronedarone) Tablets 400 mg

3. Ensure that the unit-of-use bottles have a Child Resistant Closure (CRC) per the Poison Prevention Packaging Act (PPA) of 1970 to avoid accidental ingestion of Multaq.

B. Blister Labels and Blister Carton Labeling

1. Relocate the dosage form so that it appears immediately following the established name [i.e. (Dronedarone) Tablets 400 mg].
2. The blister carton labeling includes a (b) (4) ' statement. The use of abbreviations should be avoided when possible as it may not be readily understood. Please consider revising the current net quantity statement to "10 x 10 unit dose blisters" to be in alignment with standard label/labeling nomenclature.

_3__ Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X___ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Other Reviews __3_____

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/s/

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1/13/2009 10:15:39 AM
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