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Bridgewater, New Jersey 08807

## **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

### **NDA 22-425 Multaq<sup>®</sup> (dronedarone)**

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

**I. GOALS**

- To prevent Multaq<sup>®</sup> use in patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic by educating prescribers about increased mortality when Multaq<sup>®</sup> is used in this patient population.
- To inform patients about the serious risks of Multaq<sup>®</sup>, including increased mortality in patients with severe unstable heart failure.

**II. REMS ELEMENTS**

**A. MEDICATION GUIDE**

In accordance with 21 CFR 208.24, sanofi-aventis will ensure that the Medication Guide is available for distribution to patients by providing sufficient numbers to distributors, packers, or authorized dispensers in order to provide a Medication Guide to each patient receiving a sample or a prescription of Multaq<sup>®</sup>. Sanofi-aventis will institute the following measures:

- The label of each container or package of Multaq<sup>®</sup> will include a prominent instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed.
- One copy of the Full Prescribing Information that includes a Medication Guide will be provided with each 60-count unit-of-use bottle of Multaq<sup>®</sup> (a monthly usual supply). Additional Medication Guides will be provided for the 180-count and 500-count bottles as follows:
  - A minimum of 3 Medication Guides will be provided with each 180-count bottle
  - A minimum of 9 Medication Guides will be provided with each 500-count bottle

Medication Guides will be available via sales and/or medical representatives, the product website and through the Sponsor's Medical Information Services Department.

The Medication Guide is appended to this document (see Appendix 1).

## **B. COMMUNICATION PLAN**

In accordance with FDCA 505-1(e) (3), sanofi-aventis will implement a Communication Plan to health care professionals (HCPs) to support implementation of this REMS. The purpose of the Communication Plan is to educate health care professionals on risks associated with the use of Multaq<sup>®</sup>, the safe and appropriate prescribing information, and the goals of the REMS.

The Elements of the Communication Plan include:

### *1. Health Care Professional Information Sheet*

- a. Sanofi-aventis will issue a *Health Care Professional Information Sheet* to targeted health care professionals (key stakeholders and secondary stakeholders as defined below) within 60 days of the REMS approval. This Information Sheet highlights the goals of the Multaq<sup>®</sup> REMS and actions to ensure appropriate use. Sanofi-aventis will distribute the *Health Care Professional Information Sheet* through hardcopy mailings. In addition, this information will be available through electronic communication (Health Care Notification Network [HCNN]) and made available on the product website.
- b. The *Health Care Professional Information Sheet*, Multaq<sup>®</sup> Package Insert and Medication Guide will be distributed to HCPs at product launch. These materials will be disseminated every 18 months for at least 3 years. This element of the REMS is not intended to continue over the lifetime of the product; it will function only to inform prescribers of the goals of the Multaq<sup>®</sup> REMS for a period of 3 years.

The *Health Care Professional Information Sheet* is appended to this document (see Appendix 2).

### **2. REMS Print Advertising in Professional Society Journals**

- a. Sanofi-aventis will issue REMS Print Advertisements in the following professional society journals, monthly for 24 months, following approval of the REMS:
  - i. Journal of the American College of Cardiology
  - ii. Circulation
  - iii. Annals of Internal Medicine

The REMS Print Advertisement is appended to this document (see Appendix 3).

The intended audience for the Communication Plan is:

1. Key stakeholders: Health care professionals, including cardiologists, electrophysiologists, hospitalists, internal medicine and family practice physicians who regularly prescribe antiarrhythmic agents will be targeted. Members of relevant professional societies will also be targeted.
2. Secondary stakeholders: Nurse practitioners and physician assistants who work in offices of the above-mentioned physicians will also be targeted as secondary stakeholders for education.

**C. ELEMENTS TO ASSURE SAFE USE**

Multaq<sup>®</sup> can be approved without Elements to Assure Safe Use.

**D. IMPLEMENTATION SYSTEM**

Multaq<sup>®</sup> can be used without Elements to Assure Safe Use; therefore, an implementation system is not required.

**E. TIMETABLE FOR SUBMISSION OF ASSESSMENTS**

Formal assessments of the REMS performance will be provided to the Food and Drug Administration (FDA) annually, years 1-5 and at year 7 post-launch. The first assessment interval will be from August 2009 (product launch) to June 2010. All assessment reports will be submitted to the Agency on the due date as indicated below.

<b>Assessment number</b>	<b>Submission Due Date</b>
1	August 31, 2010
2	August 31, 2011
3	August 31, 2012
4	August 31, 2013
5	August 31, 2014
6	August 31, 2016

## **APPENDICES OF REMS**

- 1. Multaq<sup>®</sup> Medication Guide**
- 2. Health Care Professional Information Sheet**
- 3. REMS Print Advertisement**

## **1. MULTAQ<sup>®</sup> MEDICATION GUIDE**

## 17.2 Medication Guide

### Medication Guide

#### MULTAQ (MUL-tak)

#### (dronedarone) Tablets

#### Rx only

Read this Medication Guide before you start taking MULTAQ and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

#### What is the most important information I should know before taking MULTAQ?

**MULTAQ is not for people with severe heart failure. People with severe heart failure who take MULTAQ have an increased chance of dying.** Heart failure means your heart does not pump blood through your body as well as it should.

#### Do not take MULTAQ if you have severe heart failure:

- **where any physical activity causes shortness of breath or you have shortness of breath while at rest or after a small amount of exercise.**
- **if you were hospitalized for heart failure within the last month even if you are better now.**

Call your doctor right away if you have any signs and symptoms of worsening heart failure:

- shortness of breath or wheezing at rest
- wheezing, chest tightness or coughing up frothy sputum at rest, nighttime or after minor exercise
- trouble sleeping or waking up at night because of breathing problems
- using more pillows to prop yourself up at night so you can breathe more easily
- gaining more than 5 pounds quickly
- increasing swelling of feet or legs

## What is MULTAQ?

MULTAQ is a prescription medicine used to lower the chance that you would need to go into the hospital for heart problems. It is meant for people who have had an abnormal heart rhythm called atrial fibrillation or atrial flutter in the last six months but who do not have that abnormal rhythm now or are about to be converted to a normal rhythm. It may be safely used for people who have had atrial fibrillation and atrial flutter who also have medical problems such as high blood pressure, stroke or diabetes.

It is not known if MULTAQ is safe and effective in children younger than age 18 years old.

## Who should not take MULTAQ?

See “What is the most important information I should know about taking MULTAQ?”

### Do not take MULTAQ if:

- **You have severe heart failure or have recently been in the hospital for heart failure, even if you are better now.**
- **You have severe liver problems.**
- **You take certain medicines that can change the amount of MULTAQ that gets into your body. Do not use these medicines with MULTAQ:**
  - Nefazodone for depression
  - Norvir<sup>®</sup> (ritonavir) for HIV infection
  - Nizoral<sup>®</sup> (ketoconazole), and Sporanox<sup>®</sup> (itraconazole), and Vfend<sup>®</sup> (voriconazole) for fungal infections
  - Ketek<sup>®</sup> (telithromycin), Biaxin<sup>®</sup> (clarithromycin) for bacterial infections
  - Cyclosporine for organ transplant
- **You take certain medicines that can lead to a dangerous abnormal heart rhythm:**
  - Some medicines for mental illness called phenothiazines
  - Some medicines for depression called tricyclic antidepressants
  - Some medicines for abnormal heart rhythm or fast heartbeat
  - Some medicines for bacterial infection

Ask your doctor if you are not sure if your medicine is one that is listed above.

- **You are pregnant or plan to become pregnant.** It is not known if MULTAQ will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- **You are breast-feeding or plan to breastfeed.** It is not known if MULTAQ passes into your breast milk. You and your doctor should decide if you will take MULTAQ or breastfeed. You should not do both.

### **What should I tell my doctor before starting MULTAQ?**

- If you have any other heart problems
- Tell your doctor about all the medicines you take, including any new medicines. Include all prescription and non-prescription medicines, vitamins and herbal remedies. MULTAQ and certain other medicines can react with each other, causing serious side effects. **Know the medicines you take.** Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

### **Be sure to tell your doctor and pharmacist if you take:**

- medicine for high blood pressure, chest pain, or other heart conditions
- statin medicine to lower blood cholesterol
- medicine for TB (tuberculosis)
- medicine for seizures
- medicine for organ transplant
- herbal supplement called St. John's wort

Some of these medicines could keep MULTAQ from working well or make it more likely for you to have side effects.

### **How should I take MULTAQ?**

- Take MULTAQ exactly as your doctor tells you.
- Take MULTAQ two times a day with food, once with your morning meal and once with your evening meal.
- Do not stop taking MULTAQ even if you are feeling well for a long time. The medicine may be working.
- If you miss a dose, wait and take your next dose at your regular time. Do not take 2 doses at the same time. Do not try to make up for a missed dose.

### **What should I avoid while taking MULTAQ?**

Do not drink grapefruit juice while you take MULTAQ. Grapefruit juice and grapefruit can increase the amount of MULTAQ in your blood and increase the likelihood that you will have a side effect of MULTAQ.

### **What are the possible side effects of MULTAQ?**

- Slowed heartbeat (bradycardia)
- Stomach problems such as
  - diarrhea
  - nausea
  - vomiting

- stomach area (abdominal) pain
- indigestion
- feeling tired and weak
- skin problems such as redness, rash, and itching

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of MULTAQ. For more information ask your doctor or pharmacist.

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

### **How should I store MULTAQ?**

Store MULTAQ at room temperature (59-86°F, or 15-30°C).

**Keep MULTAQ and all medicines out of the reach of children.**

### **General information about MULTAQ**

Medicines are sometimes used for purposes not mentioned in a Medication Guide. Do not use MULTAQ for a condition for which it was not prescribed. Do not give MULTAQ to other people, even if they have the same symptoms or condition. It may harm them.

This Medication Guide summarizes the most important information about MULTAQ. If you would like more information:

- Talk with your doctor
- Ask your doctor or pharmacist for information about MULTAQ that was written for health-care professionals
- For the latest information and Medication Guide, visit [www.sanofi-aventis.us](http://www.sanofi-aventis.us) or call sanofi-aventis Medical Information Services at 1-800-633-1610 option 1. The Medication Guide may have changed since this copy was printed.

### **What are the ingredients in MULTAQ?**

**Active ingredient:** dronedarone

**Inactive ingredients:** hypromellose, starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate polyethylene glycol 6000, titanium dioxide, carnauba wax

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Rx only

Issued month/year

Manufactured by Sanofi Winthrop Industrie

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sanofi-aventis U.S. LLC  
Bridgewater, NJ 08807

## **2. MULTAQ<sup>®</sup> HEALTH CARE PROFESSIONAL INFORMATION SHEET**

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AFib) or atrial flutter (AFL), with a recent episode of AFib/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter  $\geq 50$  mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted.

**Do not prescribe MULTAQ for patients with NYHA Class IV heart failure (HF) or NYHA Class II–III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic**

**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.**

**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.**

**Prescribers should also be aware of other important contraindications, including:**

- Coadministration of strong CYP3A4 inhibitors, medicinal products inducing Torsade de Pointes, or Class I or III antiarrhythmic agents
- Second- or third-degree atrioventricular block, sick sinus syndrome (except when used in conjunction with a functioning pacemaker), or bradycardia of <50 bpm
- QTc Bazett  $\geq 500$  ms or PR interval >280 ms
- Severe hepatic impairment
- Pregnancy or nursing mothers

## Please consider the following *Steps for Ensuring Appropriate Use* when prescribing MULTAQ for your patients:

### 1. Initiate MULTAQ in appropriate patients

- Screen patients for severity and stability of heart failure; MULTAQ should not be initiated in patients with NYHA Class IV heart failure or NYHA Class II–III heart failure with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic
- Treatment may be initiated in an outpatient or an inpatient setting
- Discontinue use of other Class I or Class III antiarrhythmic therapies
- The dosage of certain cardiovascular medications may need to be adjusted and certain laboratory test changes may occur

### 2. Counsel patients to report changes in their symptoms and their medications

- Advise patients to consult a physician if they develop signs or symptoms of worsening heart failure such as weight gain, dependent edema, and/or increasing shortness of breath
- Advise patients that MULTAQ should not be taken with certain other medications and to consult with their physicians before starting any new drugs as the dosage of certain cardiovascular medications may need to be adjusted
- Refer patients to the Medication Guide and address any additional questions

### 3. Check patients for changes in their symptoms or certain lab tests

- Observe patients regularly for signs or symptoms of heart failure that may require additional treatment and/or MULTAQ discontinuation
- Be aware that within a week, MULTAQ causes a small change in serum creatinine that does not reflect a change in underlying renal function

***In patients with developing or worsening heart failure during treatment, use clinical judgment to guide the management of each patient based on individual benefit/risk assessment, and consider the suspension or discontinuation of MULTAQ therapy.***

Please refer to the enclosed Prescribing Information for complete safety information before prescribing MULTAQ.

#### **Serious Adverse Events:**

Health care professionals should report any serious adverse events thought to be associated with MULTAQ use to:

- Sanofi-aventis at 1-800-633-1610 option 2
- FDA's MedWatch reporting system
  - By phone (1-800-FDA-1088)
  - By facsimile (1-800-FDA-0178)
  - Online (<https://www.accessdata.fda.gov/scripts/medwatch/>)
  - By mail (using the MedWatch Voluntary Reporting form 3500, to the FDA Safety Information and Adverse Event Reporting Program: Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787)

#### **Additional Resources**

For additional information:

- Talk to your sanofi-aventis sales representative or call the sanofi-aventis Medical Information Services department at 1-800-633-1610 option 1
- Visit [www.MULTAQ.com](http://www.MULTAQ.com)
- Refer patients to the MULTAQ Medication Guide

### **3. MULTAQ<sup>®</sup> REMS PRINT ADVERTISEMENT**

## Important Information on the Use of MULTAQ<sup>®</sup> (dronedarone)

**Do not prescribe MULTAQ for patients with NYHA Class IV heart failure (HF) or NYHA Class II–III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic**

### **WARNING: HEART FAILURE**

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**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.**

### **Prescribers should also be aware of other important contraindications, including:**

- Coadministration of strong CYP3A4 inhibitors, medicinal products inducing Torsade de Pointes, or Class I or III antiarrhythmic agents
- Second- or third-degree atrioventricular block, sick sinus syndrome (except when used in conjunction with a functioning pacemaker), or bradycardia of <50 bpm
- QTc Bazett  $\geq 500$  ms or PR interval >280 ms
- Severe hepatic impairment
- Pregnancy or nursing mothers

### **MULTAQ is an antiarrhythmic drug indicated to:**

- Reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AFib) or atrial flutter (AFL), with a recent episode of AFib/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter  $\geq 50$  mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted

### **Sanofi-aventis is committed to appropriate patient care and treatment**

The mPACT Program has been developed for health care professionals who will prescribe MULTAQ, in an effort to help ensure appropriate patient selection.

Visit [www.MULTAQ.com](http://www.MULTAQ.com) for more information.

Please see accompanying Brief Summary before prescribing MULTAQ.