Initial REMS Approval: July 1, 2009
Most Recent Modification: September 2012

NDA 22-425 Multaq® (dronedarone)

sanofi-aventis U.S. 55 Corporate Boulevard
Bridgewater, New Jersey 08807

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

- To prevent Multaq® use in patients with:
    - Symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure
    - Permanent atrial fibrillation (AF) that will not or cannot be cardioverted into normal sinus rhythm
- To inform healthcare professionals and patients about the serious risks of Multaq®, including:
    - Increased risk of cardiovascular death in patients with symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure
    - Increased risk of cardiovascular death, heart failure and stroke in patients with permanent AF
    - Signs and symptoms of liver injury and hepatic failure

II. REMS ELEMENTS

A. MEDICATION GUIDE

A Medication Guide will be dispensed with each Multaq® prescription, in accordance with 21 CFR 208.24.

The updated Medication Guide is part of the REMS and is appended.

B. COMMUNICATION PLAN

Sanofi-aventis will implement a Communication Plan to inform healthcare professionals (HCPs) of the risks associated with the use of Multaq®, safe and appropriate prescribing information, and the goals of the REMS.

The Communication Plan includes:

1. *Healthcare Professional Information Sheet*

a. The *Healthcare Professional Information Sheet* is intended to highlight the important safety information for Multaq. The Information Sheet provides a high-level reminder for HCPs for each point of the prescribing process: initiation of therapy, patient counseling and ongoing management and follow-up. This sheet thereby re-enforces the goals of the REMS and actions to ensure appropriate use. The Healthcare Professional Information Sheet will be posted on the REMS website within 15 days and continue for a period of 5 years after drug approval.

The *Healthcare Professional Information Sheet* is a part of the REMS and is appended.

2. *Dear Healthcare Provider Letters*

a. Important drug warning about increased risk of death, stroke and heart failure in patients with permanent atrial fibrillation treated with Multaq®. This Dear Healthcare Provider letter provided an update to an important drug warning about the increased risk of cardiovascular events and death in patients with permanent AF treated with Multaq®. Additionally, the need to discontinue Multaq® in patients who develop or progress toward permanent AF while on Multaq® was highlighted. This DHCP letter was posted on the REMS website (www.multaqrems.com) within 15 days after the approval of the permanent AF REMS modification (June 2012) and will continue for a period of 1 year from approval of that REMS modification (June 2013).

The Dear Healthcare Provider letter (permanent AF) is part of the REMS and is appended.

b. *Important drug warning about hepatic failure in patients treated with Multaq®*. This Dear Healthcare Provider letter provided an important drug warning about hepatic failure in patients treated with Multaq® and the signs and symptoms that both HCPs and patients should monitor. This DHCP letter was posted on the REMS website (www.multaqrems.com) within 15 days after the approval of the hepatic REMS modification (August 2011) and will continue for 1 year after the corresponding REMS modification approval (August 2012).

The Dear Healthcare Provider letter (hepatic) is part of the REMS and is appended.

3. *Healthcare Provider Checklist*

a. Sanofi-aventis will post the updated prescriber checklist, which provides key evaluation points for the HCP at the point of prescribing, to the REMS website within 15 days of this REMS modification approval. The Checklist will assist the HCP in the identification of contraindications for use as well as highlight the warnings and precautions for use when considering treatment with Multaq®. The Healthcare Provider Checklist will also be made available via sales and/or medical representatives and through the Sponsor's Medical Information Services Department.

The updated Healthcare Provider Checklist is part of the REMS and is appended.

4. *REMS Print Advertising in Professional Society Journals*

a. Sanofi-aventis issued REMS Print Advertisements for approximately 30 months in each of the following professional society journals since product approval:

i. Journal of the American College of Cardiology

ii. Circulation

iii. Annals of Internal Medicine

REMS Print Advertisements have been discontinued as the 24 month commitment was met.

5. *The REMS website*

a. Sanofi-aventis will ensure the REMS webpage, www.multaqrems.com, includes a link to the updated REMS materials as well as the two following FDA Drug Safety Communications: Severe liver injury associated with the use of dronedarone (marketed as Multaq) [1/14/2011] and Review update of Multaq (dronedarone) and increased risk of death and serious cardiovascular adverse events [12/19/2011]. The REMS webpage will be available for 5 years after drug approval.

The REMS website is part of the REMS and is appended.

C. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Sanofi-aventis will submit REMS Assessments to the FDA annually for years 1-5 and at year 7. All assessment reports are due on the 31st of August. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for the assessment. Sanofi-aventis will submit each assessment so that it will be received by the FDA on or before the due date.

1. MEDICATION GUIDE

17.2 Medication Guide

Medication Guide
MULTAQ (MUL-tak)
(dronedarone)
Tablets

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 about MULTAQ?

MULTAQ can cause serious side effects.

Do not take MULTAQ if you:

1. **have symptoms of heart failure that recently worsened and you were hospitalized, or if you have severe heart failure.**

   MULTAQ doubles your risk of dying if you have these conditions.
   Heart failure means your heart does not pump blood through your body as well as it should.

Call your doctor right away if you have any signs or symptoms of heart failure during treatment with MULTAQ:

- 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

2. **have a type of atrial fibrillation (irregular heart rhythm) called permanent atrial fibrillation (AF).**
   You and your doctor may decide not to try to change your heart rhythm back to a normal heart rhythm or your heart rhythm cannot be changed back to a normal rhythm. If you have permanent AF and take MULTAQ, you have a higher risk of death, stroke, and needing to be treated in a hospital for your heart failure.

   Your doctor will monitor your heart rhythm regularly to make sure your heartbeat keeps a normal rhythm.

Call your doctor right away if you notice that your pulse is irregular during treatment with MULTAQ. This is a sign that you are in atrial fibrillation.

MULTAQ may cause liver problems, including life-threatening liver failure. Your doctor may order blood tests to check your liver before you start taking MULTAQ and during treatment. In some cases MULTAQ treatment may need to be stopped.

Call your doctor right away if you develop any of these signs and symptoms of liver problems during treatment with MULTAQ:

- loss of appetite, nausea, vomiting
- fever, feeling unwell, unusual tiredness
- itching
- yellowing of the skin or the whites of the eyes (jaundice)
- unusual darkening of the urine
- right upper stomach area pain or discomfort

What is MULTAQ?

MULTAQ is a prescription medicine used to lower the chance that you will need to go into the hospital for atrial fibrillation. It is meant for people who have had certain types of atrial fibrillation (paroxysmal or persistent AF) in the past, but are now in normal rhythm.

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 a certain type of heart problem called heart block, and you do not have an implanted pacemaker**
- **you have a slow heart rate, less than 50 beats each minute**
- **you have severe liver problems or had liver or lung problems after using amiodarone (a medicine for abnormal heart rhythm)**
- **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® (ritonavir) for HIV infection
  - Nizoral® (ketoconazole), and Sporanox® (itraconazole), and Vfend® (voriconazole) for fungal infections
  - Ketek® (telithromycin), Biaxin® (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.

  - Women who may become pregnant should use effective birth control (contraception) while taking MULTAQ. Talk to your doctor about the best birth control methods for you.

- **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.

- **You are allergic to dronedarone or any of the other ingredients in MULTAQ**. See the end of this Medication Guide for a complete list of ingredients in MULTAQ.

What should I tell my doctor before taking MULTAQ?

Before taking MULTAQ, tell your doctor if you:
- have any other heart problems
- Have any other medical conditions

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. MULTAQ and certain other medicines can react with each other, causing serious side effects.

Especially 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
- digoxin (Lanoxin)
- warfarin (Coumadin, Jantoven), a blood thinner medicine
- medicine for organ transplant
- herbal supplement called St. John's wort

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

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 without first talking to your doctor, even if you are feeling well for a long time.
- 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.
- If you take too much MULTAQ, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking MULTAQ?
Do not drink grapefruit juice while you are being treated with MULTAQ. Grapefruit juice 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?

MULTAQ may cause serious side effects, including:

- **See "What is the most important information I should know about MULTAQ?"**
- **Slowed heartbeat (bradycardia)**
- **Inflammation of the lungs, including scarring and thickening**. Call your doctor if you develop shortness of breath or a dry cough during treatment with MULTAQ.
- **Low potassium and magnesium levels in your blood.** This can happen if you take certain water pills (diuretics) during treatment with MULTAQ. Your doctor may check you for this problem before and during treatment.
- **Changes in kidney function blood tests after starting MULTAQ**. Your doctor may check you for this during treatment.

The most common side effects of MULTAQ include:
- 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 other than those listed 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 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.

Issued July 2012
Manufactured by Sanofi Winthrop Industrie
1, rue de la Vierge
33440 Ambares, France

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

2. MULTAQ® HEALTHCARE PROFESSIONAL INFORMATION SHEET

RISK MITIGATION PROGRAM

MPACT™

MULTAQ® Partnership for Appropriate Care and Treatment

Health Care Professional Information Sheet for MULTAQ® (dronedarone)

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of hospitalization for AFib in patients in sinus rhythm with a history of paroxysmal or persistent AFib. Multaq is available in 400-mg tablets.

FDA has required a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of MULTAQ outweigh the risks.

Boxed Warning

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

MULTAQ is contraindicated in patients in atrial fibrillation (AFib) who will not or cannot be cardioverted into normal sinus rhythm. In patients with permanent AFib, MULTAQ doubles the risk of death, stroke, and hospitalization for heart failure.

MULTAQ doubles the risk of death and is therefore contraindicated in the following populations:

- **Permanent atrial fibrillation:** Patients treated with MULTAQ should undergo monitoring of cardiac rhythm no less often than every 3 months. Cardiovert patients who are in AFib (if clinically indicated) or discontinue MULTAQ. MULTAQ offers no benefit in subjects in permanent AFib. In this population, MULTAQ was associated with an increased risk of stroke, particularly in the first two weeks of therapy. MULTAQ should only be initiated in patients in sinus rhythm who are receiving appropriate antithrombotic therapy
- **Symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure**

For a complete list of contraindications, please refer to the prescribing information, including boxed WARNING.

In the postmarketing setting, the following REMS-related risks have been reported:

- **New onset or worsening heart failure:** In a placebo-controlled study in patients with permanent AFib, 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. If heart failure develops or worsens and requires hospitalization, discontinue MULTAQ
- **Hepatocellular liver injury, including acute liver failure requiring transplant:** 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

RISK MITIGATION PROGRAM
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for Appropriate Care and Treatment

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

1. Appropriate Patient Selection

- Screen patients for severity and stability of 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
- MULTAQ is contraindicated in patients with permanent AFib that will not or cannot be cardioverted into normal sinus rhythm
- MULTAQ should only be initiated in patients in sinus rhythm who are receiving appropriate antithrombotic therapy. In a placebo-controlled study in patients with permanent AFib, MULTAQ was associated with an increased risk of stroke, particularly in the first two weeks of therapy
- STOP treatment with Class I or III antiarrhythmics (e.g., amiodarone, flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol) or drugs that are strong inhibitors of CYP 3A (e.g., ketoconazole) before starting MULTAQ
- The dosage of certain cardiovascular medications may need to be adjusted and certain laboratory test changes may occur. These cardiovascular medications include statins, calcium-channel blockers, sirolimus, tacrolimus, beta-blockers, and other CYP 2D6 substrates, digoxin, dabigatran, and warfarin

2. Patient Monitoring

- Observe patients for new onset or worsening of heart failure. If heart failure develops or worsens and requires hospitalization, discontinue MULTAQ® (dronedarone)
- Patients treated with dronedarone should undergo monitoring of cardiac rhythm no less often than every 3 months. Cardiovert patients who are in AFib (if clinically indicated) or discontinue MULTAQ. MULTAQ offers no benefit in patients in permanent AFib
- Monitor patients for signs and symptoms of liver injury. 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
- Patients should be carefully evaluated clinically for pulmonary toxicity. If confirmed, treatment should be discontinued
- Renal function should be monitored periodically in patients treated with MULTAQ as increases in creatinine and blood urea nitrogen have been reported in the postmarketing setting and appear to be reversible after discontinuation of MULTAQ

RISK MITIGATION PROGRAM

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3. Patient Counseling

- 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
- Advise patients to immediately report symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching) to their physician
- 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 medication may need to be adjusted
- Refer patients to the Medication Guide and address any additional questions

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, or visit www.multaqrems.com.

Alternatively, report this information to FDA's MedWatch reporting system by phone (1-800-FDA-1088), facsimile (1-800-FDA-0178), online (https://www.accessdata.FDA.gov/scripts/medwatch/), or mail using the MedWatch for FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Additional Resources

For additional information, talk to your sanofi-aventis sales representative, call sanofi-aventis Medical Information Services department at 1-800-633-1610, option 1, or visit www.multaqrems.com. Additionally, refer patients to the MULTAQ Medication Guide.

For full prescribing information, including boxed WARNING, please see enclosed PI or refer to the link on www.multaqrems.com, the site from which this page was downloaded.

US.DRO.12.03.009 March 2012

SANOFI

3. DEAR HEALTHCARE PROFESSIONAL LETTERS

A. PERMANENT AFIB DHCPL

December 2011

IMPORTANT DRUG WARNING

SANOFI

Increased Risk of Death, Stroke and Heart Failure in Patients with Permanent Atrial Fibrillation treated with Multaq (Dronedarone)

Dear Healthcare Provider:

In August 2011, Sanofi communicated preliminary information on the premature termination of the PALLAS (Permanent Atrial fibriLLAtion outcome Study using Dronedarone on top of standard therapy) study due to increased risk of CV death, stroke, and heart failure events.

Following adjudication and final analysis of the PALLAS data and subsequent update and FDA-approval of the United States Prescribing Information (USPI), Sanofi would like to provide you with highlights of the important updates to the Multaq USPI pertaining to PALLAS and permanent atrial fibrillation (AF).

In addition to an update to the heart failure contraindication, the boxed warning for Multaq has been expanded to include permanent AF (AF patients who will not or cannot be cardioverted into normal sinus rhythm). The boxed warning now reads as follows:

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

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.

The following has also been added to the **WARNINGS AND PRECAUTIONS** section of the Multaq USPI:

5 WARNING AND PRECAUTIONS

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. MULTAQ should only be initiated in patients in sinus rhythm who are receiving appropriate antithrombotic therapy.

Additionally, the indication for Multaq has been updated to help ensure its appropriate use in paroxysmal or persistent atrial fibrillation (i.e. non-permanent AF patients). **Multaq is indicated to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation (AF).**

In accordance with these changes, the Multaq Medication Guide has been updated to include this information. **We encourage you to discuss the new important safety information outlined in this letter and the updated Multaq USPI and Medication Guide with your patients** (the link to the current Prescribing Information, including Medication Guide, has been provided below for your review).

Also of note, Sanofi is collaborating with the FDA to appropriately update the Multaq Risk Evaluation and Mitigation Strategy (REMS). You will be notified of the changes to the Multaq REMS program once it is FDA-approved.

Please note the information above does not contain all changes to the Multaq USPI. Please refer to the full Prescribing Information for Multaq for complete details.

For additional information, please contact Sanofi Medical Information Services at 1-800-633-1610 (option 1). Healthcare professionals should report adverse events suspected to be associated with the use of Multaq to Sanofi at 1-800-633-1610 (option 2).

Alternatively, report this information to 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/) or mailed, using the MedWatch for FDA 3500, to the FDA Medical Products Reporting Program,
5600 Fishers Lane, Rockville, MD 20852-9787.

Sincerely,

Paul H. Chew, M.D.

Paul H. Chew, MD
US Chief Science Officer/Chief Medical Officer
sanofi-aventis U.S.

Click here for full Prescribing Information, including Boxed Warning.
This letter was prepared with the guidance of FDA.

B. HEPATIC DHCPL

Initial Release: January 14, 2011
Revised to reflect updated Prescribing Information and REMS: June 2011

IMPORTANT DRUG WARNING

sanofi aventis
Because health matters

Hepatic Failure in Patients Treated with Multaq (Dronedarone)

Dear Healthcare Provider:

The purpose of this letter is to inform you of new important safety information for Multaq®, an antiarrhythmic. Multaq® was approved in July 2009 with an FDA required Risk Evaluation and Mitigation Strategy (REMS). The REMS has been modified to include informing healthcare professionals and patients about the serious risks of liver injury and hepatic failure with Multaq®.

Several cases of hepatocellular liver injury and hepatic failure have occurred in patients receiving Multaq (dronedarone), including two post-marketing reports of acute hepatic failure requiring transplantation. Multaq is indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent history of AF/AFL and associated cardiovascular risk factors (age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥ 50 mm or left ventricular ejection fraction <40%) who are in sinus rhythm or who will be cardioverted.

Healthcare professionals should advise patients treated with Multaq to immediately report symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching) and should 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, Multaq should be promptly discontinued and testing of serum enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase, as well as the serum bilirubin, should be performed to establish whether there is liver injury. If liver injury is found, appropriate treatment should be instituted and investigations should be performed to establish the probable cause. Multaq should not be restarted in patients without another explanation for the observed liver injury.

sanofi-aventis U.S., 55 Corporate Drive, PO Box 5925, Bridgewater, NJ 08807-0890
Tel. (908) 981-5000 – www.sanofi-aventis.com

The two cases of acute hepatic failure requiring transplantation occurred at 4.5 and 6 months after initiation of Multaq in patients with previously normal hepatic serum enzymes. Both patients were female and approximately 70 years of age.

In the first case, the patient had underlying intermittent atrial fibrillation, arterial hypertension and stable coronary artery disease. She was treated with Multaq for 4.5 months. Two weeks prior to hospitalization she reported increased exhaustion and tiredness. One week prior to admission she discontinued Multaq, and at the time of admission she was noted to have jaundice, coagulopathy, transaminitis and hyperbilirubinemia, which progressed to hepatic encephalopathy over the next nine days. A pre-transplant workup did not reveal another etiology of liver failure.

In the second case, the patient had a medical history of paroxysmal atrial fibrillation and Sjögren's syndrome. Following 6 months of treatment with Multaq she developed weakness, abdominal pain, coagulopathy, transaminitis and hyperbilirubinemia. She was transplanted 1 month later; no alternative etiology for liver failure was identified in the transplant work-up. In both cases, the explanted liver showed evidence of extensive hepatocellular necrosis.

The Prescribing Information for Multaq has been revised to include this information (the link to the current Prescribing Information has been provided below for your information). **We encourage you to discuss the new important safety information outlined in this letter with your patients.**

Healthcare professionals should report cases of hepatic injury and failure or any serious adverse events suspected to be associated with the use of Multaq to sanofi-aventis at 1-800-633-1610 (option 2).

Alternatively, report this information to 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/) or mailed, using the MedWatch for FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Sincerely,

Paul H. Chew, MD
US Chief Science Officer/Chief Medical Officer
sanofi-aventis U.S.

Click here for full Prescribing Information, including Boxed Warning.
This letter was prepared with the guidance of FDA.

4. HEALTHCARE PROVIDER CHECKLIST

MULTAQ® (Dronedarone) Health Care Professional Checklist

RISK MITIGATION PROGRAM
MPACT
MULTAQ® Partnership for Appropriate Care and Treatment

This checklist is intended to assist health care professionals with identifying the appropriate patients for MULTAQ.

MULTAQ is indicated to reduce the risk of hospitalization for atrial fibrillation (AFib) in patients in sinus rhythm with a history of paroxysmal or persistent AFib. MULTAQ is available in 400-mg tablets.

The following are contraindications for use with MULTAQ.
Permanent AFib that will not or cannot be cardioverted into normal sinus rhythm
Symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure
2nd or 3rd degree 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
Concomitant use of drugs or herbal products that prolong the QT interval and might increase the risk of Torsade de Pointes, such as phenothiazine antipsychotics, tricyclic antidepressants, certain oral macrolide antibiotics, and Class I and III antiarrhythmics
Liver or lung toxicity related to the previous use of amiodarone
A QTc Bazett interval ≥500 ms or PR interval >280 ms
Severe hepatic impairment
Pregnancy (Category X): patients who are or may become pregnant
Nursing mothers
Hypersensitivity to the active substance or to any of the excipients

The following information was derived from WARNINGS and PRECAUTIONS	
• Cardiac rhythm should be monitored (≤q3 months)	• Potassium should be within normal range prior to and maintained in the normal range during administration of MULTAQ
• MULTAQ should only be initiated in patients in sinus rhythm who are receiving appropriate antithrombotic therapy	• Onset of dyspnea or non-productive cough may be related to pulmonary toxicity and patients should be carefully evaluated clinically
• Advise patients to consult a physician if they develop signs or symptoms of heart failure	• Monitor renal function periodically
• Consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment	

For full Prescribing Information, including boxed WARNING, please see enclosed PI or refer to the link on multaqrems.com, the site from which this page was downloaded.

US.DRO.12.03.010 March 2012

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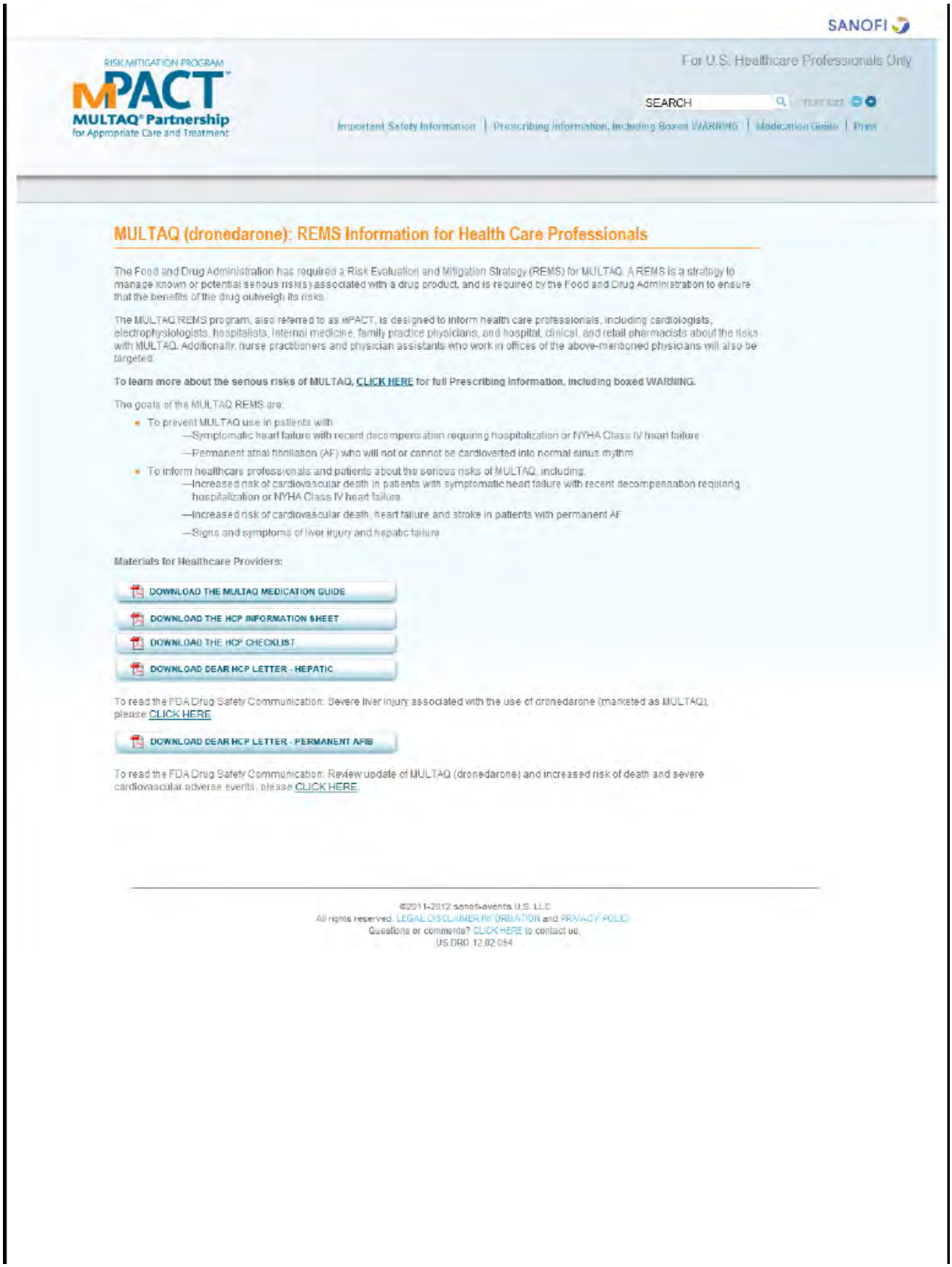
5. THE REMS WEBSITE



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RISK MITIGATION PROGRAM
MPACT
MULTAQ® Partnership for Appropriate Care and Treatment

For U.S. Healthcare Professionals Only

SEARCH

Important Safety Information | Prescribing Information, including Boxed WARNING | Medication Guide | Print

MULTAQ (dronedarone): REMS Information for Health Care Professionals

The Food and Drug Administration has required a Risk Evaluation and Mitigation Strategy (REMS) for MULTAQ. A REMS is a strategy to manage known or potential serious risk(s) associated with a drug product, and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

The MULTAQ REMS program, also referred to as iPACT, is designed to inform health care professionals, including cardiologists, electrophysiologists, hospitalists, internal medicine, family practice physicians, and hospital, clinical, and retail pharmacists about the risks with MULTAQ. Additionally, nurse practitioners and physician assistants who work in offices of the above-mentioned physicians will also be targeted.

To learn more about the serious risks of MULTAQ, CLICK HERE for full Prescribing Information, including boxed WARNING.

The goals of the MULTAQ REMS are:

- To prevent MULTAQ use in patients with
  - —Symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure
  - —Permanent atrial fibrillation (AF) who will not or cannot be cardioverted into normal sinus rhythm
- To inform healthcare professionals and patients about the serious risks of MULTAQ, including:
  - —Increased risk of cardiovascular death in patients with symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure
  - —Increased risk of cardiovascular death, heart failure and stroke in patients with permanent AF
  - —Signs and symptoms of liver injury and hepatic failure

Materials for Healthcare Providers:

DOWNLOAD THE MULTAQ MEDICATION GUIDE
DOWNLOAD THE HCP INFORMATION SHEET
DOWNLOAD THE HCP CHECKLIST
DOWNLOAD DEAR HCP LETTER - HEPATIC

To read the FDA Drug Safety Communication: Severe liver injury associated with the use of dronedarone (marketed as MULTAQ), please CLICK HERE

DOWNLOAD DEAR HCP LETTER - PERMANENT AFIB

To read the FDA Drug Safety Communication: Review update of MULTAQ (dronedarone) and increased risk of death and severe cardiovascular adverse events, please CLICK HERE.