

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.

**FDA has required a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of MULTAQ outweigh the risks of heart failure and liver injury and hepatic failure.**

### **Boxed Warning for Heart Failure:**

#### **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 MULTAQ had a greater than two-fold increase in mortality. Such patients should not be given MULTAQ.**

Postmarketing cases of new onset and worsening heart failure have been reported during treatment with MULTAQ. Advise patients to consult with a physician if they develop signs or symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath. If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ.

### **Risk of Liver Injury, Including Life-Threatening Acute Liver Failure:**

- Advise patients treated with MULTAQ to report immediately symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching).
- If liver 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 probable cause. Do not restart MULTAQ in patients without another explanation for the observed liver injury.

## Contraindications:

Prescribers should be aware that MULTAQ® is also contraindicated in patients with:

- Second- or third-degree atrioventricular block, sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Bradycardia <50 bpm
- Concomitant use with strong CYP 3A inhibitors such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, ritonavir
- Concomitant use of drugs or herbal products that prolong the QT interval and may induce Torsade de Pointes, such as phenothiazine anti-psychotics, tricyclic antidepressants, certain oral macrolide antibiotics, and Class I and III antiarrhythmic agents
- QTc Bazett  $\geq$ 500 msec or PR interval >280 msec
- Severe hepatic impairment
- Pregnancy (Category X)
- Nursing mothers

## 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 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.
- STOP treatment with Class I or III antiarrhythmics (e.g., amiodarone, flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol) or drugs that are strong inhibitors of CYP3A (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 CYP 2D6 substrates, digoxin, dabigatran, and warfarin.

### 2. Patient Monitoring

- Observe patients for new or worsening heart failure, as both of these have been reported during treatment with MULTAQ.
- Monitor patients for signs and symptoms of liver injury. 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.
- MULTAQ has been associated with increases in serum creatinine.

### 3. Patient Counseling

- Advise patients to consult a physician if they develop signs or symptoms of new or worsening heart failure such as weight gain, dependent edema, and/or increasing shortness of breath.
- Advise patients to immediately report symptoms suggestive of hepatic injury such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching.
- 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

Healthcare 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](http://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](http://www.multaqrems.com). Additionally, refer patients to the MULTAQ Medication Guide.