

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.

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 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

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 who 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 renal failure have been reported in the postmarketing setting. In most cases, these effects appear to be reversible after discontinuation of MULTAQ

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 accompanying full 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.

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 by mail using the MedWatch Form FDA 3500, addressed to FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Additional Resources

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

Important Safety Information for MULTAQ® (dronedarone)

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 is also contraindicated in patients:

- With second- or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker), bradycardia <50 bpm, QTc Bazett interval \geq 500 ms or PR interval >280 ms
- Who are or may become pregnant (Category X) or nursing. MULTAQ may cause fetal harm when administered to a pregnant woman
- With concomitant use of strong CYP 3A inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, ritonavir, or 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
- With liver or lung toxicity related to the previous use of amiodarone
- With severe hepatic impairment
- With hypersensitivity to the active substance or to any of the excipients

Cardiovascular Death in NYHA Class IV or Decompensated 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.

Cardiovascular Death and Heart Failure in Permanent AFib

MULTAQ doubles the risk of cardiovascular death (largely arrhythmic) and heart failure events in patients with permanent AFib. 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.

Increased Risk of Stroke in Permanent AFib

In a placebo-controlled study in patients with permanent AFib, 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.

New Onset or Worsening Heart Failure

New onset or worsening of heart failure has been reported during treatment with MULTAQ in the postmarketing setting. 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.

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. If heart failure develops or worsens and requires hospitalization, discontinue MULTAQ.

Liver Injury

Hepatocellular liver injury, including acute liver failure requiring transplant, has been reported in patients treated with MULTAQ in the postmarketing setting. 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). 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, 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.

Pulmonary Toxicity

Cases of interstitial lung disease including pneumonitis and pulmonary

fibrosis have been reported in patients treated with MULTAQ in the post-marketing setting. Onset of dyspnea or non-productive cough may be related to pulmonary toxicity and patients should be carefully evaluated clinically. If pulmonary toxicity is confirmed, MULTAQ should be discontinued.

Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics

Hypokalemia and hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics. Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ.

QT Interval Prolongation

MULTAQ induces a moderate (average of about 10 ms but much greater effects have been observed) QTc (Bazett) prolongation. If the QTc Bazett interval is \geq 500 ms, discontinue MULTAQ.

Renal Impairment and Failure

Marked increase in serum creatinine, pre-renal azotemia and acute renal failure, often in the setting of heart failure or hypovolemia, have been reported in patients taking MULTAQ. In most cases, these effects appear to be reversible upon drug discontinuation and with appropriate medical treatment. Monitor renal function periodically.

Small increases in creatinine levels (about 0.1 mg/dL) following MULTAQ treatment initiation have been shown to be a result of inhibition of creatinine's tubular secretion. The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation.

Women of Childbearing Potential

Premenopausal women who have not undergone a hysterectomy or oophorectomy must use effective contraception while using MULTAQ. Dronedarone caused fetal harm in animal studies at doses equivalent to recommended human doses. Counsel women of childbearing potential regarding appropriate contraceptive choices.

Drug-Drug Interactions

- Treatment with Class I or III antiarrhythmics or drugs that are strong inhibitors of CYP 3A must be stopped before starting MULTAQ (see Contraindications)
- Patients should be instructed to avoid grapefruit juice beverages while taking MULTAQ
- Calcium channel blockers with depressant effects and beta-blockers could increase the bradycardia effects of MULTAQ on conduction
- In the ANDROMEDA (patients with recently decompensated heart failure) and PALLAS (patients with permanent AFib) trials, baseline use of digoxin was associated with an increased risk of arrhythmic or sudden death in MULTAQ-treated patients compared to placebo. In patients not taking digoxin, no difference in risk of sudden death was observed in the MULTAQ vs placebo groups
- Digoxin can potentiate the electrophysiologic effects of MULTAQ (such as decreased AV-node conduction). MULTAQ increases exposure to digoxin. Consider discontinuing digoxin. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity
- Postmarketing cases of increased INR with or without bleeding events have been reported in warfarin-treated patients initiated with MULTAQ. Monitor INR after initiating MULTAQ in patients taking warfarin
- Statins: Avoid simvastatin doses greater than 10 mg daily. Follow statin label recommendations for use with CYP 3A and P-gP inhibitors such as MULTAQ

Adverse Reactions

In studies, the most common adverse reactions observed with MULTAQ were diarrhea, nausea, abdominal pain, vomiting, and asthenia.

For full Prescribing Information, including boxed WARNING, please [click here](#) or visit [MULTAQ.com/hcp](#).