MAINTAIN SINUS RHYTHM LONGER1∗

MULTAQ kept patients in sinus rhythm 2.2 times longer than placebo

• 116 days vs 53 days, respectively

Reduced risk of 1st AFib recurrence by 25%

(relative risk; \(P<0.001\))

• Absolute difference in rate of 1st recurrence at Year 1 for MULTAQ vs placebo was 11%
• Majority of 1st recurrences were symptomatic

62.3% of patients were free of symptomatic AFib recurrence at Year 1 vs 54% of patients on placebo

• Symptomatic AFib recurrence included 1 or more of the following symptoms: palpitations, dizziness, fatigue, chest pain, and dyspnea

ONLY AAD PROVEN TO REDUCE AFIB AND CV HOSPITALIZATION1,2,3†

39% relative risk reduction of AFib-related hospitalization

(HR=0.61; 95% CI=0.53-0.71; \(P<0.0001\))

- Hospitalization rates: 12.7% with MULTAQ vs 19.6% with placebo
- AFib hospitalization was a component of the secondary endpoint of CV hospitalization1 (26% RRR, \(HR=0.74; 95\% CI=0.67-0.82; P<0.0001\))
- Hospitalization rates were 29.1% with MULTAQ vs 36.8% with placebo

24% relative risk reduction of combined endpoint of CV-related hospitalization or all-cause mortality, entirely attributable to reduction in CV hospitalization (HR=0.76; 95% CI=0.68-0.83; \(P<0.0001\))

- Hospitalization/mortality rates: 31.6% with MULTAQ vs 39.2% with placebo

AFIB GUIDELINE RECOMMENDED AS A 1ST-LINE THERAPY—AHA/ACC/HRS4

Joint clinical practice guideline for the management of atrial fibrillation (AFib) recommends MULTAQ as a 1st-line therapy to maintain sinus rhythm in patients with coronary artery disease or without structural heart disease.

SAFETY AND TOLERABILITY PROFILE2

- Most frequent adverse reactions (>2%) with MULTAQ vs placebo: diarrhea (9% vs 6%), nausea (5% vs 3%), abdominal pain (4% vs 3%), vomiting (2% vs 1%), asthenia (7% vs 5%), respectively
- Premature discontinuation due to adverse reactions: 11.8% with MULTAQ vs 7.7% with placebo
- Most common reasons for discontinuation of therapy with MULTAQ vs placebo: gastrointestinal disorders (3.2% vs 1.8%) and QT prolongation (1.5% vs 0.5%)

AAD = antiarrhythmic drug.

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**Indication**

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of hospitalization for atrial fibrillation (AFib) in patients in sinus rhythm with a history of paroxysmal or persistent AFib.

**Important Safety Information for MULTAQ® (dronedarone)—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 with 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.

*Pooled data from 2 identical, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials (12 months; \(N=1237\); \(n=828\) in MULTAQ arms; \(n=409\) in placebo arms). Primary endpoint was time to first symptomatic or asymptomatic recurrence of AFib/AFL. Secondary endpoint was incidence of symptomatic first AFib recurrence.1

†Data from a prospective, randomized, placebo-controlled, double-blind, multinational, multicenter, parallel-group trial (30-month maximum duration; \(N=4628\); \(n=2301\) in MULTAQ arm; \(n=2327\) in placebo arm). Primary endpoint was time to first CV hospitalization, or death from any cause (results entirely attributable to effect on CV hospitalization, principally related to AFib; \(P<0.0001\)). Secondary endpoints were CV hospitalization (\(P<0.0001\)) and all-cause mortality (\(P=NS\)).1,3

Please see additional Important Safety Information on next page. For full Prescribing Information, including boxed WARNING, please click here or visit MULTAQ.com/hcp.
MULTAQ doubles the risk of cardiovascular death (largely in heart failure) 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 of hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching). Consider obtaining periodic blood tests during MULTAQ treatment to monitor hepatic 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 ≥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 heart failure 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 3A4 and P-gp inhibitors such as MULTAQ

Dronedarone caused 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 Points, 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.

IMPORTANT SAFETY INFORMATION FOR MULTAQ® (dronedarone)

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