For paroxysmal or persistent AFib patients new to rhythm control therapy

SUPPORT

MULTAQ Savings Cards available for commercially insured patients

- Samples and Patient Assistance Program also available

PROVEN

MULTAQ with meals can ensure a therapeutic dose[1]

- MULTAQ 400 mg BID should be taken with full morning and evening meals
- **~4x greater** bioavailability with food than without food
- After initial administration, steady state is reached within **4 to 8 days**

OUTPATIENT INITIATION

Approved for outpatient initiation[1]

- No hospital admission required
- No continuous ECG monitoring
- No loading dose or titration

Monitoring considerations[1]

- No specific assessment of thyroid or lung function is required with MULTAQ
- Patients treated with MULTAQ should undergo monitoring of cardiac rhythm no less often than every 3 months
- Consider obtaining periodic liver enzymes, especially during first 6 months of treatment
- Monitor renal function periodically

(See Important Safety Information on next page for additional monitoring considerations)

RECOMMENDED

A first-line therapy in the 2014 AHA/ACC/HRS AFib Guidelines[2]

- Recommended to maintain sinus rhythm in patients with paroxysmal or persistent AFib with coronary artery disease or without structural heart disease

EXPERIENCE

Treatment experience[3]

- More than **4.8 million prescriptions** filled to date
- MULTAQ has been commercially available in the US **since 2009**

CV hospitalization*[,1,4]

- Reduced the combined endpoint of CV hospitalization or death from any cause by **24% RRR**,† entirely attributable to reduction in CV hospitalization (HR 0.76; 95% CI 0.68-0.83; *P*<0.0001)
- Incidence of primary endpoint events was 31.6% with MULTAQ vs 39.2% with placebo
- Most CV hospitalizations were AFib related

Proven antiarrhythmic efficacy‡[,5]

- **62.3%** of patients free of symptomatic AFib recurrence vs 54% on placebo at 1 year (*P*<0.001)
- Kept patients in sinus rhythm **2.2x longer** than placebo (116 days vs 53 days, respectively)
- **25% RRR** (*P*<0.001) of first AFib recurrence (symptomatic or asymptomatic). Absolute difference in recurrence rate of about 11% at 1 year. Majority of first recurrences were symptomatic

Safety and tolerability profile[1]

- Most frequent adverse reactions (≥2%) with MULTAQ vs placebo in 5 clinical studies: 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 in clinical trials: 11.8% with MULTAQ vs 7.7% with placebo
- Most common reasons for discontinuation with MULTAQ vs placebo: GI disorders (3.2% vs 1.8%) and QT prolongation (1.5% vs 0.5%), respectively

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 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.

*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; *P*<0.0001). Secondary endpoints were CV hospitalization (*P*<0.0001) and all-cause mortality (*P*=NS).[1,4]

†Relative risk reduction (RRR) observed over the study period (median 22-month treatment and follow-up; minimum 12 months, maximum 30 months).[1,4]

‡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.[5]

Please see additional Important Safety Information on next page. For full Prescribing Information, including boxed WARNING, please click here or visit MULTAQ.com/hcp.

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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 ≥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 ≥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.

References: 1. MULTAQ® (dronedarone) Prescribing Information. Bridgewater, NJ: sanofi-aventis U.S. LLC. **2.** January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64(21):e1-e76. **3.** IMS Health, National Prescription Audit™. July 2009-October 2015. **4.** Hohnloser SH, Crijns HJGM, van Eickels M, et al; for the ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med.* 2009;360(7):668-678. **5.** Singh BN, Connolly SJ, Crijns HJGM, et al; for the EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med.* 2007;357(10):987-999.

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