DOSAGE AND ADMINISTRATION

One tablet of 400 mg twice a day with morning and evening meals (2)

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of hospitalization for atrial fibrillation (AF) in patients in sinus rhythm with a history of paroxysmal or persistent AF (1, 14).

DOSAGE FORMS AND STRENGTHS

400 mg film-coated tablets (3)

CONTRAINDICATIONS

- Permanent AF (patients in whom normal sinus rhythm will not or cannot be restored) (Boxed Warning, 4)
- Recently decompensated heart failure requiring hospitalization or Class IV heart failure. (Boxed Warning, 4)
- Second or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker) (4)
- Bradycardia <50 bpm (4)
- Concomitant use of a strong CYP3A inhibitor (4)
- Concomitant use of drugs or herbal products that prolong the QT interval and may induce Torsade de Pointes (4)
- Liver or lung toxicity related to the previous use of amiodarone (4)
- Severe hepatic impairment (4)

WARNINGS AND PRECAUTIONS

- Cardiovascular Death in NYHA Class IV or Decompensated Heart Failure
- Increased Risk of Stroke in Permanent AF
- Enhanced Risk of Death, Stroke, and Hospitalization for Heart Failure
- Hypokalemia and Hypomagnesemia
-QTc Bazett interval ≥500 ms (4)
- Pregnancy (4, 8.1) and Nursing mothers (4, 8.3)
-Hypersensitivity to the active substance or to any of the excipients (4)

ADVERSE REACTIONS

Most common adverse reactions (≥2%) are diarrhea, nausea, abdominal pain, vomiting, and asthenia (5)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Dronedarone is metabolized by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6 and has potentially important pharmacodynamic interactions (7)

- Class I or III Antiarrhythmics: contraindicated (4, 7.1)
- Diclofenac: Consider discontinuation or halve dose of diclofenac before treatment and monitor diclofenac levels (7.1, 7.3)
- Calcium channel blockers (CCB): Initiate CCB with low dose and increase after ECG verification of tolerability (7.1, 7.2, 7.3)
- Beta-blockers: May provoke excessive bradycardia. Initiate with low dose and increase after ECG verification of tolerability (7.1, 7.3)
- CYP3A inducers: Avoid concomitant use (7.2)
- Grapefruit juice: Avoid concomitant use (7.2)
- Statins: Avoid simvastatin doses greater than 10 mg daily. Follow label recommendations for concomitant use of other statins with a CYP3A and P-gp inhibitor like dronedarone (7.3)
- CYP3A substrates with a narrow therapeutic index (e.g., sirolimus and tacrolimus): Monitor and adjust dosage of concomitant drug as needed when used with MULTAQ (7.3)
- Warfarin: Monitor INR after initiating dronedarone in patients taking warfarin. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2017
In a placebo-controlled study in patients with permanent atrial fibrillation, dronedarone was associated with more frequent than placebo:

- Bradycardia 1% 2%
- Diarrhea 6% 9%
- Asthenic conditions 5% 7%
- Vomiting 1% 2%
- Bradycardia 1% 3%
- Pulmonary toxicity 1% 3%
- Hypokalemia and hypomagnesemia with potassium-depleting diuretics [see Warnings and Precautions (5.6)]
- QT prolongation [see Warnings and Precautions (5.8)]

The following safety concerns are described elsewhere in the label:
- New or worsening heart failure [see Warnings and Precautions (5.4)]
- Liver Injury [see Warnings and Precautions (5.5)]
- Pulmonary toxicity [see Warnings and Precautions (5.6)]
- Hypokalemia and hypomagnesemia with potassium-depleting diuretics [see Warnings and Precautions (5.6)]
- QT prolongation [see Warnings and Precautions (5.8)]

5.6 Pulmonary Toxicity

Cases of intestinal lung disease including pneumonitis and pulmonary fibrosis have been reported in patients treated with MULTAQ in the postmarketing setting. [see Adverse Reactions (6.2)]. 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.

5.7 Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics

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

5.8 QT Interval Prolongation

Dronedarone induces a moderate (average of about 10 ms but much greater effects have been observed) QTC [Bazett] prolongation [see Clinical Pharmacology (12.2), Clinical Studies (14.1)]. If the QTC Bazett interval is >500 ms, discontinue MULTAQ [see Contraindications (4)].

5.9 Renal Impairment and Failure

Marked increase in serum creatinine, pre-renal azotemia and acute renal failure, often in the setting of heart failure [see Warnings and Precautions (5.4)] 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 dronedarone 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.

5.10 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 relevant to recommended human doses of 30-75 mg/day. MULTAQ doubles the risk of congenital anomalies in women of childbearing potential regarding appropriate contraceptive choices [see Use in Specific Populations (8.1)].

6. ADVERSE REACTIONS

The safety evaluation of dronedarone 400 mg twice daily in patients with AF or AFL is based on 5 placebo controlled studies, ATHENA, EURIDIS, ADONIS, ERAPO and DAFNE. In these studies, a total of 6285 patients were randomized and treated, 3282 patients with MULTAQ 400 mg twice daily, and 2873 with placebo. The mean exposure across studies was 12 months. In ATHENA, the maximum follow-up was 30 months.

In clinical trials, premature discontinuation because of adverse reactions occurred in 11.8% of the dronedarone-treated patients and in 7.7% of the placebo-treated group. The most common reasons for discontinuation of therapy with MULTAQ were gastrointestinal disorders (3.2 % versus 1.8 % in the placebo group) and QT prolongation (1.5% versus 0.5% in the placebo group).

The most frequent adverse reactions observed with MULTAQ 400 mg twice daily in the 5 studies were diarrhea, nausea, abdominal pain, vomiting, and asthenia.

Table 1 displays adverse reactions more common with dronedarone 400 mg twice daily than with placebo in AF or AFL patients, presented by system organ class and by decreasing order of frequency. Adverse laboratory and ECG effects are presented separately in Table 2.

Table 1: Adverse Drug Reactions that Occurred in at Least 1% of Patients and were More Frequent than Placebo

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo</th>
<th>Dronedarone 400 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=2875)</td>
<td>(N=3282)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Dyspeptic signs and symptoms</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic conditions</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Including rashes (generalized, macular, maculo-papular, erythematous), pruritus, eczema, dermatitis, dermatitis allergic</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Photosensitivity reaction and dysgeusia have also been reported at an incidence less than 1% in patients treated with MULTAQ.
Table 2: Laboratory Data/ECG Parameters Not Necessarily Reported as Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>MULTAQ 400 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=2875)</td>
<td>(N=3282)</td>
<td></td>
</tr>
<tr>
<td>Early increases in creatinine ≥10%</td>
<td>21%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>(N=2377)</td>
<td>(N=2701)</td>
</tr>
<tr>
<td>QTc prolonged</td>
<td>19%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Assessment of demographic factors such as gender or age on the incidence of treatment-emergent adverse events did not suggest an excess of adverse events in any particular subgroup.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MULTAQ. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac: New or worsening heart failure [see Warnings and Precautions (5.4)].

Hepatic: Liver injury [see Warnings and Precautions (5.5)].

Respiratory: Interstitial lung disease including pneumonitis and pulmonary fibrosis [see Warnings and Precautions (5.6)].

Immune: Anaphylactic reactions including angioedema.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions

Drugs Potracting the QT Interval (Inducing Torsade de Pointes)

Co-administration of drugs prolonging the QT interval (such as certain phenothiazines, tricylic antidepressants, certain macrolide antibiotics, and Class I antiarrhythmics) is contraindicated because of the potential risk of torsade de pointes-type ventricular tachycardia [see Contraindications (4), Clinical Pharmacology (12.3)].

Digoxin: If the ANDROMEDA (patients with recently decompensated heart failure) and PALLAS (patients with heart failure with reduced ejection fraction) trials baseline use of digoxin was associated with an increased risk of arrhythmic or sudden death in dronedarone-treated patients compared to placebo. In patients not taking digoxin, any difference in risk of sudden death was observed in the dronedarone versus placebo group [see Clinical Studies (14.3)].

Digoxin can potentiate the electrophysiologic effects of dronedarone (such as decreased AV-node conduction). Dronedarone increases exposure to digoxin [see Drug Interactions (7.3), Clinical Pharmacology (12.3)].

Consider discontinuing digoxin if digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity.

Calcium Channel Blockers

Calcium channel blockers with depressant effects on the sinus and AV nodes could potentiate dronedarone’s effects on conduction.

Give a low dose of calcium channel blockers initially and increase only after ECG verification of good tolerability [see Drug Interactions (7.3), Clinical Pharmacology (12.3)].

Beta-Blockers

In clinical trials, bradycardia was more frequently observed when dronedarone was given in combination with beta-blockers.

Give a low dose of beta-blockers initially, and increase only after ECG verification of good tolerability [see Drug Interactions (7.3), Clinical Pharmacology (12.3)].

7.2 Effects of Other Drugs on Dronedarone

Ketoconazole and Other Potent CYP 3A Inhibitors

Concomitant use of ketoconazole as well as other potent CYP 3A inhibitors such as itraconazole, voriconazole, ritonavir, clarithromycin, and nefazodone is contraindicated because exposure to dronedarone is significantly increased [see Contraindications (4), Clinical Pharmacology (12.3)].

Grapefruit Juice

Patients should avoid grapefruit juice beverages while taking MULTAQ because exposure to dronedarone is significantly increased [see Clinical Pharmacology (12.3)].

Rifampin and Other CYP 3A Inducers

Avoid rifampin or other CYP 3A inducers such as phenobarbital, carbamazepine, phenytoin, and St. John’s wort because they decrease exposure to dronedarone significantly [see Clinical Pharmacology (12.3)].

7.3 Effects of Dronedarone on Other Drugs

Simvastatin

Dronedarone increased simvastatin/simvastatin acid exposure. Avoid doses greater than 10 mg once daily of simvastatin [see Clinical Pharmacology (12.3)].

Other Statins

Because of multiple mechanisms of interaction with statins (CYPs and transporters), follow statin label recommendations for use with CYP 3A and P-gp inhibitors such as dronedarone.

Calcium Channel Blockers

Dronedarone increased the exposure of calcium channel blockers (verapamil, diltiazem, or nifedipine).

Give a low dose of calcium channel blockers initially and increase only after ECG verification of good tolerability [see Drug Interactions (7.1), Clinical Pharmacology (12.3)].

Siroloimus, Tacrolimus, and Other CYP3A Substrates with Narrow Therapeutic Range

Dronedarone can increase plasma concentrations of sirolimus, tacrolimus, and other CYP 3A substrates with a narrow therapeutic range when given orally. Monitor plasma concentrations and adjust dosage appropriately.

Beta-Blockers and Other CYP2D6 Substrates

Dronedarone increased the exposure of propranolol and metoprolol. Give low doses of beta-blockers initially, and increase only after ECG verification of good tolerability. Other CYP2D6 substrates, including other beta-blockers, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) may have increased exposure upon coadministration with dronedarone [see Drug Interactions (7.1), Clinical Pharmacology (12.3)].

P-glycoprotein Substrates

Digoxin

Dronedarone increased digoxin exposure by inhibiting the P-gp transporter. Consider discontinuing or reducing the dose of digoxin, monitor serum levels closely, and observe for toxicity [see Drug Interactions (7.1), Clinical Pharmacology (12.3)].

Dabigatran

Exposure to dabigatran is higher when it is administered with dronedarone than when it is administered alone.

Other P-gp substrates are expected to have increased exposure when coadministered with dronedarone.

Warfarin

When coadministered with dronedarone exposure to S-warfarin was slightly higher than when warfarin was administered alone. There were no clinically significant increases in INR [see Clinical Pharmacology (12.3)].

More patients experienced clinically significant INR elevations (≥ 5) usually within 1 week after dronedarone versus placebo in patients taking oral anticoagulants in ATHENA. However, no excess risk of bleeding was observed in the dronedarone group.

Postmarketing cases of increased INR with or without bleeding events have been reported in warfarin-treated patients initiated on dronedarone. Monitor INR after initiating dronedarone in patients taking warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see Contraindications (4)]

MULTAQ may cause fetal harm when administered to a pregnant woman. In animal studies, dronedarone was teratogenic in rats at the maximum recommended human dose (MRHD), and in rabbits at half the MRHD. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

When pregnant rats received dronedarone at oral doses greater than or equal to the MRHD (on a mg/m² basis), fetuses had increased rates of external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactyly, syndactyly, and anterior and/or posterior club foot). When pregnant rabbits received dronedarone, at a dose approximately half the MRHD (on a mg/m² basis), fetuses had an increased rate of skeletal abnormalities (anomalous ribcage and vertebral, pelvic asymmetry) at doses ≥20 mg/kg (the lowest dose tested and approximately half the MRHD on a mg/m² basis). Actual animal doses: rat (=80 mg/kg/day); rabbit (=220 mg/kg).

8.3 Nursing Mothers

It is not known whether MULTAQ is excreted in human milk. Dronedarone and its metabolites are excreted in rat milk. During a prenatal and postnatal study in rats, maternal dronedarone administration was associated with minor reduced body-weight gain in the offspring. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MULTAQ, discontinue nursing or discontinue the drug [see Contraindications (4)].

8.4 Pediatric Use

Safety and efficacy in children below the age of 18 years have not been established.

8.5 Geriatric Use

More than 4500 patients with AF or AFL aged 65 years or above were included in the MULTAQ clinical program (of whom more than 2000 patients were 75 years or older). Efficacy and safety were similar in elderly and younger patients.

8.6 Renal Impairment

Patients with renal impairment were included in clinical studies. Because renal excretion of dronedarone is minimal [see Clinical Pharmacology (12.3)], no dosing alteration is needed.

8.7 Hepatic Impairment

Dronedarone is extensively metabolized by the liver. There is little clinical experience with moderate hepatic impairment and none with severe impairment. No dosage adjustment is recommended for moderate hepatic impairment [see Contraindications (4), Clinical Pharmacology (12.3)].

10 OVERDOSAGE

In the event of overdose, monitor the patient’s cardiac rhythm and blood pressure. Treatment should be supportive and based on the patient’s condition.

It is not known whether dronedarone or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis or hemofiltration).

There is no specific antidote available.

11 DESCRIPTION

Dronedarone HCl is a benzenoid derivative with the following chemical name: N-2(2-butyl)-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl) methanesulfonamide, hydrochloride.

Dronedarone HCl is a white powder that is practically insoluble in water and freely soluble in methylene chloride and methanol.

Its empirical formula is C₂₉H₂₈N₂O₄·HCl with a molecular mass of 593.2. Its structural formula is:

MULTAQ is provided as tablets for oral administration. Each tablet of MULTAQ contains 400 mg of dronedarone (expressed as base).

The inactive ingredients are:

- Core of the tablets: hypromellose, starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate.
- Coating/polishing of the tablets: hypromellose, polyethylene glycol 6000, titanium dioxide, carnauba wax.
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
The mechanism of action of dronedarone is unknown. Dronedarone has antiarrhythmic properties belonging to all four Vaughan-Williams antiarrhythmic classes, but the contribution of each of these activities to the clinical effect is unknown.

12.2 Pharmacodynamics

Electrophysiological Effects

Dronedarone exhibits properties of all four Vaughan-Williams antiarrhythmic classes, although it is unclear which of these are important in producing dronedarone’s clinical effects. The effect of dronedarone on ECG parameters (heart rate, PR, and QT) was investigated in healthy subjects following repeated oral doses up to 1600 mg once daily or 800 mg twice daily for 14 days and 1600 mg twice daily for 10 days. In the dronedarone 400 mg twice-daily group, there was no apparent effect on heart rate; a moderate heart rate lowering effect (about 4 bpm) was noted at 800 mg twice daily. There was a clear dose-dependent effect on PR-interval with an increase of +5 ms at 400 mg twice daily and up to +50 ms at 1600 mg twice daily. There was a moderate dose related effect on the QTc-interval with an increase of +10 ms at 400 mg twice daily and up to +25 ms with 1600 mg twice daily.

DAPNE Study

DAPNE was a dose-response study in patients with recurrent AF, evaluating the effect of dronedarone in comparison with placebo in maintaining sinus rhythm. The doses of dronedarone in this study were 400, 600, and 800 mg twice a day. In this small study, doses above 400 mg were not more effective and were less well tolerated.

12.3 Pharmacokinetics

Dronedarone is extensively metabolized and has low systemic bioavailability; its bioavailability is increased by meals. Its elimination half life is 13–19 hours.

Absorption

Because of presystemic first pass metabolism the absolute bioavailability of dronedarone without food is low, about 4%. It increases to approximately 15% when dronedarone is administered with a high fat meal. After oral administration in fed conditions, peak plasma concentrations of dronedarone and the main circulating active metabolite (N-debutyl metabolite) are reached within 3 to 6 hours. After repeated administration of 400 mg twice daily, steady state is reached within 4 to 8 days of treatment and the mean accumulation ratio for dronedarone ranges from 2.6 to 4.5. The steady-state Cmax and exposure of the main N-debutyl metabolite is similar to that of the parent compound. The pharmacokinetics of dronedarone and its N-debutyl metabolite both deviate moderately from dose proportionality: a 2-fold increase in dose results in an approximate 2.5 to 3.0-fold increase with respect to Cmax and AUC.

Distribution

The in vitro plasma protein binding of dronedarone and its N-debutyl metabolite is >98% and not saturable. Both compounds bind mainly to albumin. After intravenous (IV) administration the volume of distribution at steady state is about 1400 L.

Metabolism

Dronedarone is extensively metabolized, mainly by CYP3A. The initial metabolic pathway includes N-debutylation to form the active N-debutyl metabolite, oxidative deamination to form the inactive propanoic acid metabolite, and direct oxidation. The metabolites undergo further metabolism to yield over 30 uncharacterized metabolites. The N-debutyl metabolite exhibits pharmacodynamic activity but is 1/10 to 1/3 as potent as dronedarone. Monoamine oxidases contribute partially to the metabolism of the active metabolite of dronedarone.

Excretion/Elimination

In a mass balance Study with orally administered dronedarone (14C-labeled) approximately 6% of the labeled dose was excreted in urine, mainly as metabolites (no unchanged compound excreted in urine), and 84% was excreted in feces, mainly as metabolites. Dronedarone and its N-debutyl metabolite both deviate moderately from dose proportionality: a 2-fold increase in dose results in an approximate 2.5 to 3.0-fold increase with respect to Cmax and AUC.

The clinical effect of dronedarone has not been assessed.

Gender

Dronedarone exposures are on average 30% higher in females than in males. Race

Pharmacokinetic differences related to race were not formally assessed. However, based on a cross study comparison, following single dose administration (400 mg), Asian males (Japanese) have about 14% lower maximum plasma concentration and 13% lower AUC compared to Caucasian males.

Elderly

Of the total number of subjects in clinical studies of dronedarone, 73% were 65 years of age and over, and 44% were 75 and over. In patients aged 65 years old and above, dronedarone exposures are 23% higher than in patients less than 65 years old [see Use in Specific Populations (8.5)]

Hepatic impairment

In subjects with moderate hepatic impairment, the mean dronedarone exposure increased by 1.3 fold relative to subjects with normal hepatic function and the mean exposure of the N-debutyl metabolite decreased by about 50%. Pharmacokinetic data were significantly more variable in subjects with moderate hepatic impairment.

The effect of severe hepatic impairment on the pharmacokinetics of dronedarone was not assessed [see Contraindications (4)].

Renal impairment

Consistent with the low renal excretion of dronedarone, no pharmacokinetic difference was observed in subjects with mild or moderate renal impairment compared to subjects with normal renal function [see Use in Specific Populations (8.6)]

In vitro data indicate that SR90154 is likely to inhibit the organic anion transporters OAT1 and OAT3 or the organic cation transporter OCT1. However, in vitro data indicate that SR90154 is likely to inhibit the organic anion transporting polypeptides (OATP1B1, OATP1B3) in vivo.

Pharmacokinetic measures indicating the magnitude of these interactions are presented in Figure 1 (impact of coadministered drugs on dronedarone) and Figure 2 (impact of dronedarone on coadministered drug).
14 CLINICAL STUDIES

14.1 ATHENA

ATHENA was a multicenter, multinational, double-blind, and randomized placebo-controlled study of dronedarone in 4628 patients with a recent history of AF/AFL who were in sinus rhythm or who were to be converted to sinus rhythm. The objective of the study was to determine whether dronedarone could delay death from any cause or hospitalization for cardiovascular reasons.

Initially patients were to be ≥70 years old, or <70 years old with at least one risk factor (including hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or LVEF <30%). The inclusion criteria were later changed such that patients were to be ≥75 years old, or ≥70 years old with at least one risk factor. Patients had to have both AF/AFL and sinus rhythm documented within the previous 6 months. Patients could have been in AF/AFL or in sinus rhythm at the time of randomization, but patients not in sinus rhythm were expected to be either electrically or chemically converted to normal sinus rhythm after anticoagulation.

Subjects were randomized and treated for up to 30 months (median follow-up: 22 months) with either MULTAQ 400 mg twice daily (2301 patients) or placebo (2327 patients), in addition to conventional therapy for cardiovascular diseases that included beta-blockers (71%), ACE inhibitors or angiotensin II receptor blockers (ARBs) (69%), digoxin (14%), calcium antagonists (14%), statins (39%), oral anticoagulants (60%), aspirin (44%), other chronic antiplatelet therapy (6%) and diuretics (54%).

The primary endpoint of the study was the time to first hospitalization for cardiovascular reasons or death from any cause. Time to death from any cause, time to first hospitalization for cardiovascular reasons, and time to cardiovascular death and time to all causes of death were also explored. Patients ranged in age from 23 to 97 years; 42% were 75 years old or older. Forty-seven percent (47%) of patients were female and a majority was Caucasian (89%). Seventy-one percent (71%) of those could delay death from any cause or hospitalization for cardiovascular reasons.

Patients not in sinus rhythm at randomization were expected to be either electrically or chemically converted to normal sinus rhythm after anticoagulation.

The reduction in cardiovascular hospitalization or death from any cause was generally consistent in all subgroups based on baseline characteristics or medications (ACE inhibitors or ARBs; beta-blockers, digoxin, statins, calcium channel blockers, diuretics) (see Figure 4).

Table 3: Incidence of Endpoint Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>MULTAQ 400 mg twice daily</th>
<th>HR</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular hospitalization or death from any cause</td>
<td>913 (39.2%)</td>
<td>727 (31.6%)</td>
<td>0.76</td>
<td>[0.68-0.83]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>57 (2.4%)</td>
<td>58 (2.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Components of the endpoint (as first event)**

- Cardiovascular hospitalization
- Death from any cause
- Components of the cardiovascular hospitalization endpoint (as first event)
  - AF and other supraventricular rhythm disorders
  - Other

**Secondary endpoints (any time in study)**

- Death from any cause
- Cardiovascular hospitalization

**Components of the cardiovascular hospitalization endpoint (as first event)**

- AF and other supraventricular rhythm disorders
- Other

The Kaplan-Meier cumulative incidence curves showing the time to first event are displayed in Figure 3. The event curves separated early and continued to diverge over the 30 month follow-up period.

Figure 3: Kaplan-Meier Cumulative Incidence Curves from Randomization to First Cardiovascular Hospitalization or Death from Any Cause

Reasons for hospitalization included major bleeding (1% in both groups), syncope (1% in both groups), and ventricular arrhythmia (<1% in both groups).

14.2 EURIDIS and ADONIS

In EURIDIS and ADONIS, a total of 1237 patients in sinus rhythm with a prior episode of AF or AFL were randomized in an outpatient setting and treated with either MULTAQ 400 mg twice daily (n=628) or placebo (n=609) on top of conventional therapies (including oral anticoagulants, beta-blockers, ACE inhibitors or ARBs, chronic antiplatelet agents, diuretics, statins, digoxin, and calcium channel blockers). Patients had at least one ECG-documented AF/AFL episode during the 3 months prior to study entry but were in sinus rhythm for at least one hour. Patients ranged in age from 20 to 88 years, with the majority being Caucasian (97%), male (70%) patients. The most common comorbidities were hypertension (56.8%) and structural heart disease (41.5%), including coronary heart disease (21.8%). Patients were followed for 12 months.

In the pooled data from EURIDIS and ADONIS as well as in the individual trials, dronedarone delayed the time to first recurrence of AF/AFL (primary endpoints), lowering the risk of first AF/AFL recurrence during the 12-month study period by about 25%, with an absolute difference in recurrence rate of about 11% at 12 months.

14.3 ANDROMEDA

Patients recently hospitalized with symptomatic heart failure and severe left ventricular systolic dysfunction (wall motion index ≤1.2) were randomized to either MULTAQ 400 mg twice daily or matching placebo, with a primary composite end point of all-cause mortality or hospitalization for heart failure. Patients enrolled in ANDROMEDA were predominantly NYHA Class II (40%) and III (57%), and only 25% had AF at randomization. After enrollment of 627 patients and a median follow-up of 63 days, the trial was terminated because of excess mortality in the dronedarone group. Twenty-five (25) patients in the dronedarone group died versus 12 patients in the placebo group (hazard ratio 2.13; 95% CI 1.07 to 4.25). The main reason for death was worsening heart failure. Baseline digoxin therapy was reported in 6/16 dronedarone patients versus 1/16 placebo patients who died of arrhythmia. In patients without baseline use of digoxin, no excess risk of arrhythmic death was observed in the dronedarone versus placebo groups.

There were also excess hospitalizations for cardiovascular reasons in the dronedarone group (71 vs 51 for placebo) (see Boxed Warning, Contraindications (4)).
14.4 PALLAS

Patients with permanent AF (AF documented in 2 weeks prior to randomization and at least 6 months prior to randomization in whom cardioversion had failed or was not planned) and additional risk factors for thromboembolism (coronary artery disease, prior stroke or TIA, symptomatic heart failure, LVEF <40%, peripheral arterial occlusive disease, or age >75 with hypertension and diabetes) were randomized to dronedarone 400 mg twice daily or placebo.

After enrollment of 3236 patients (placebo=1617 and dronedarone=1619) and a median follow up of 3.7 months for placebo and 3.9 for dronedarone, the study was terminated because of a significant increase in

- Mortality: 25 dronedarone versus 13 placebo (HR, 1.94; CI: 0.99 to 3.79). The majority of deaths in the dronedarone group were classified as arrhythmic/sudden deaths (HR, 3.26; CI: 1.06 to 10.0).
- Baseline digoxin therapy was reported in 11/13 dronedarone patients who died of arrhythmia. None of the arrhythmic deaths on placebo (4) reported use of digoxin. In patients without baseline use of digoxin, no excess risk of arrhythmic death was observed in the dronedarone versus placebo groups.
- Stroke: 23 dronedarone versus 10 placebo (HR, 2.32; CI: 1.11 to 4.88). The increased risk of stroke observed with dronedarone was observed in the first two weeks of therapy (10 dronedarone vs 1 placebo), most of the subjects treated with dronedarone did not have an INR of 2.0 to 3.0 [see Warnings and Precautions (5.3)].
- Hospitalizations for heart failure in the dronedarone group: 43 dronedarone versus 24 placebo (HR, 1.81; CI: 1.10 to 2.92).

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
- swelling of the skin or the whites of the eyes (jaundice)
- unusual darkening of 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 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
  - Kefek® (teithroctimycin), 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 not allowed to be used with MULTAQ.

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 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. You 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