**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use MULTAQ safely and effectively. See full prescribing information for MULTAQ.

MULTAQ® (dronedarone) tablets, for oral use

**INDICATIONS AND USAGE**

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of hospitalization for atrial fibrillation (AF) in patients in whom normal sinus rhythm will not or cannot be restored. (1, 14)

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

**CONTRAINDICATIONS**

- Pregnancy (4, 8.1) and Nursing mothers (4, 8.3)
- Concomitant use of drugs or herbal products that prolong the QT interval and may induce torsade de pointes (4)
- Concomitant use of a strong CYP3A inhibitor (4)
- Liver or lung toxicity related to the previous use of amiodarone (4)

**FULL PRESCRIBING INFORMATION: CONTENTS**

**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 patients. (4, 5.1, 14.3)

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. (4, 5.1, 14.3)

**ADVERSE REACTIONS**

- Most common adverse reactions (≥2%) are diarrhea, nausea, abdominal pain, vomiting, and asthenia (6)
- 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 CYP3A and is a moderate inhibitor of CYP3A and CYP2D6 and has potentially important pharmacodynamic interactions (7)

- Warfarin: Monitor INR after initiating dronedarone in patients taking warfarin. (7.3)

**PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed.*

Revised: 11/2020
5.6 Pulmonary Toxicity
Cases of intestinal lung disease including pneumonitis and pulmonary fibrosis have been reported in patients treated with MULTAQ [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. Potassium 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 contraceptive 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 [see Use in Specific Populations (8.1)].

6. ADVERSE REACTIONS

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 (5.8)]
QT prolongation [see Warnings and Precautions (5.8)].

6.1 Clinical Trials Experience
The safety evaluation of dronedarone 400 mg twice daily in patients with AF or AFL is based on 5 placebo-controlled studies, ATHENA, EUROLISIS, ADONIS, ERATO and DAINE. In these studies, a total of 6285 patients were randomized and treated, 3282 patients with MULTAQ 400 mg twice daily, and 2875 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% vs 1.8% in the placebo group) and QT prolongation (1.5% vs 0.5% in the placebo group).

The most frequent adverse reactions observed with MULTAQ 400 mg twice daily in the 5 studies were diaphoresis, 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><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</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><strong>Dyspeptic signs and symptoms</strong></td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic conditions</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue</strong></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>

Photosensitivies reaction and dysgeusia have also been reported at an incidence less than 1% in patients treated with MULTAQ. The following laboratory data/ECG parameters were reported with MULTAQ 400 mg twice daily.
Other Statins
Simvastatin
Beta-Blockers
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 digoxin. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity [see Drug Interactions (7.1), Clinical Pharmacology (12.3)].

Dabigatran
Dronedarone increases dabigatran plasma exposures by inhibiting the P-gp transporter [see Clinical Pharmacology (12.3)]. In patients with moderate renal impairment ([CrCl] 30–50 mL/min), reduce the dose of dabigatran to 75 mg twice daily when concomitantly administered with dronedarone. In patients with severe renal impairment ([CrCl] 15–30 mL/min), concomitant use of dronedarone with dabigatran should be avoided.

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 starting 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 mice 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 (crani-schisis, cleft palate, incomplete evagination of pinnal bone, brachygnathia, partially fused carolid arteries, trunca arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactyly, syndactyly, and anterior and/or posterior club feet). 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 arrangement 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 (≥20 mg/kg/day); rabbit (≥20 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, discontinuing 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 adjustment 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 symptoms.

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

There is no specific antidote available.

11 DESCRIPTION
Dronedarone HCI is a benzofuran derivative with the following chemical name: N-2-butyl-3-[4-[3-(4-dibutylaminophenoxo)benzoyl]benzofuran-5-y] methanesulfonamide, hydrochloride. Dronedarone HCI is a white fine powder that is practically insoluble in water and freely soluble in methylene chloride and methanol.

Its empirical formula is C<sub>31</sub>H<sub>44</sub>N<sub>2</sub>O<sub>5</sub>. S, HCI with a relative 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, polaxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate.
- Coating/polishing of the tablets: hypromellose, polyethylene glycol 6000, titanium dioxide, carnuba wax.

Table 2: Laboratory Data/ECG Parameters Not Necessarily Reported as Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>MULTAQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=2875)</td>
<td>(N=2882)</td>
</tr>
<tr>
<td>Early increases in creatinine ≥10%</td>
<td>21%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>(N=2237)</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 possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
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 classes, but the contribution of each of these activities to the clinical effect is unknown.

12.2 Pharmacokinetics

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 12-lead ECG parameters (heart rate, PR, and QTc) 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.

DAFNE Study

DAFNE 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 to 19 hours.

Absorption

Because of pre-systemic 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 the pharmacokinetics 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.

Elimination

In a multiple-dose study with orally administered dronedarone (400 mg once daily) 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 accounted for less than 15% of the resultant radioactivity in plasma. After IV administration the plasma clearance of dronedarone ranges from 130 to 150 L/h.

Special Populations

Gender

Dronedarone exposures are on average 30% higher in females than in males. Treatment differences related to gender were not formally assessed. However, based on a cross study comparison, following single dose administration (400 mg), Asian males (Japanese) have about twice the clearance of dronedarone and its N-debutyl active metabolite of dronedarone.

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 a higher clearance of dronedarone and its N-debutyl active metabolite of dronedarone. The elimination half-life of dronedarone ranges from 13 to 19 hours.

Elderly

Of the total number of subjects in clinical studies of dronedarone, 73% were 65 years of age and over and 34% 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 to severe renal impairment compared to subjects with normal renal function [see Use in Specific Populations (8.6)]. No pharmacokinetic difference was observed in patients with mild to severe renal impairment in comparison with patients with normal renal function.

Drug Interactions

Dronedarone is extensively metabolized primarily by CYP3A and is a moderate inhibitor of CYP3A and CYP2D6. Dronedarone has no significant potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2C8 and CYP2B6. It has the potential to inhibit P-glycoprotein (P-gp) transport. Dronedarone inhibits in vivo the tubular secretion of creatinine a substrate of the organic cation transporter (OCT2) [see Warnings and Precautions (5.9)]. In vitro data indicate that S90154 is likely to inhibit the organic anion transporting polypeptides (OATP1B1, OATP1B3) in vivo.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In studies in which dronedarone was administered to rats and mice for up to 2 years at doses of up to 70 mg/kg/day and 300 mg/kg/day, respectively, there was an increased incidence of histiocytic sarcoma in the carpall-crenulated male mouse (300 mg/kg/day or 5× the maximum recommended human dose based on AUC comparisons), mammary adenocarcinomas in dronedarone-treated female mice (300 mg/kg/day or 8× MRHD based on AUC comparisons) and hemangiosarcoma in dronedarone-treated male rats (70 mg/kg/day or 5× MRHD based on AUC comparisons). Dronedarone did not demonstrate genotoxic potential in the in vivo mouse micronucleus test, the Ames bacterial mutation assay, the unscheduled DNA synthesis assay, or an in vitro chromosomal aberration assay in human lymphocytes. S-9 processed dronedarone, however, was positive in a V79 transfected Chinese hamster V79 assay.

In fertility studies conducted with female rats, dronedarone given prior to breeding and implantation caused an increase in irregular estrus cycles and cessation of cycling at doses ≥10 mg/kg (equivalent to 0.12 x the MRHD on a mg/m² basis). Corpora lutea, implantations and live fetuses were decreased at 100 mg/kg (equivalent to 1.2 x the MRHD on a mg/m² basis). There were no reported effects on mating behavior or fertility of male rats at doses of up to 100 mg/kg.

13.2 Developmental Toxicity

Dronedarone was teratogenic in rats given oral doses ≥80 mg/kg/day (a dose equivalent to the MRHD on a mg/m² basis), with fetuses showing external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pinell bone, brachygnathia, partially fused carotid
arteries, truncus arteriosus, abnormal location of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactyly, syndactyly, and anterior and/or posterior club feet). In rabbits, dronedarone caused an increase in skeletal abnormalities (anomalous ribcage and vertebrae, pelvic asymmetry) at doses ≥20 mg/kg (the lowest dose tested and approximately half the MRHD on a mg/m² basis).

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.

Patients were randomized to either dronedarone 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 (8%) 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 enrolled had no history of heart failure. The median ejection fraction was 60%. Twenty-nine percent (29%) of patients had heart failure, mostly NYHA class II (17%). The majority had hypertension (86%) and structural heart disease (60%).

Results are shown in Table 3. MULTAQ reduced the combined endpoint of cardiovascular hospitalization or death from any cause by 24.2% when compared to placebo. This difference was entirely attributable to its effect on cardiovascular hospitalization, primarily hospitalization related to AF.

Other endpoints, death from any cause and first hospitalization for cardiovascular reasons, are shown in Table 3. Secondary endpoints count all first events of a particular type, whether or not they were preceded by a different type of event.

Table 3: Incidence of Endpoint Events

<table>
<thead>
<tr>
<th>Endpoint Event</th>
<th>Placebo</th>
<th>MULTAQ 400 mg</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 (51.6%)</td>
<td>0.76</td>
<td>[0.68–0.83]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Secondary endpoints (any time in study)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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>
<tr>
<td>Cardiovascular hospitalization</td>
<td>856 (36.8%)</td>
<td>669 (29.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Components of the endpoint (as first event)

- Cardiovascular hospitalization:
  - Death from any cause: 57 (2.4%) vs. 58 (2.5%)

Components of the hospitalization endpoint (as first event)

- AF and other supraventricular rhythm disorders: 456 (19.6%) vs. 292 (12.7%)
  - Other: 400 (17.2%) vs. 377 (16.4%)

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).

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, calcium channel blockers, diuretics), see Table 3.

Figure 4: Relative Risk (MULTAQ vs Placebo) Estimates with 95% Confidence Intervals According to Selected Baseline Characteristics: First Cardiovascular Hospitalization or Death from Any Cause.
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 3238 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, 1.91; CI: 1.10 to 3.30).

2. have a type of atrial fibrillation (irregular heart rhythm) called permanent atrial fibrillation (AF).

You and your doctor may decide not to try to change your heart rhythm back to a normal heart rhythm or your heart rhythm cannot be changed back to a normal rhythm. If you have permanent AF and take MULTAQ, you have a higher risk of death, stroke, and needing to be treated in a hospital for your heart failure.

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
- yellowing of the skin or the whites of the eyes (jaundice)
- unusual darkening of the 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 a 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
  - Telithromycin and 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 listed above.

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 breastfeeding or plan to breastfeed. It is not known if MULTAQ passes into your breast milk. You and your doctor 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°F–86°F or 15°C–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
- For the latest information and Medication Guide, visit www.sanofi-aventis.us or call sanofi-aventis Medical Information Services at 1-800-633-1610 option 1. The Medication Guide may have changed since this copy was printed.

What are the ingredients in MULTAQ?

Active ingredient: dronedarone

Inactive ingredients: hypromellose, starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate, polyethylene glycol 6000, titanium dioxide, carnauba wax

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Manufactured by:

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SÁNOFI COMPANY

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