

## PRODUCT INFORMATION

### MULTAQ<sup>®</sup>

#### WARNING: HEART FAILURE

MULTAQ is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II - III heart failure with a recent decompensation requiring hospitalisation (see CONTRAINDICATIONS and PRECAUTIONS).

In a placebo-controlled study in patients with severe heart failure requiring recent hospitalisation for worsening symptoms (the ANDROMEDA Study), patients given dronedarone had a greater than two-fold increase in mortality. Such patients should not be given dronedarone (see CLINICAL TRIALS).

If heart failure develops or worsens in any patient, consider the suspension or discontinuation of MULTAQ (see PRECAUTIONS).

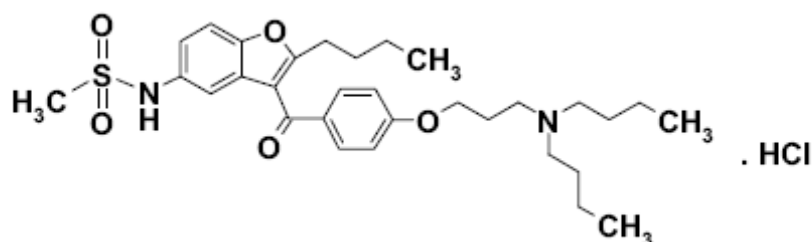
### NAME OF THE MEDICINE

#### Non-proprietary Name

Dronedarone hydrochloride.

#### Chemical Structure

Dronedarone hydrochloride is described chemically as *N*-{2-butyl-3-[4-(3-dibutylaminopropoxy) benzoyl] benzofuran-5-yl} methanesulfonamide, hydrochloride. Its empirical formula is C<sub>31</sub>H<sub>44</sub>N<sub>2</sub>O<sub>5</sub>S.HCl and the chemical structure of dronedarone hydrochloride is:



#### CAS Number

141625-93-6.

### DESCRIPTION

Dronedarone hydrochloride is a white, to practically white, fine powder with a molecular weight of 593.22. It is practically insoluble in water and soluble in ethanol and methylene chloride. MULTAQ is available for oral use as a film-coated tablet containing 400 mg of dronedarone (as hydrochloride). MULTAQ tablets also contain the following inactive ingredients: hypromellose, starch - maize, crospovidone, poloxamer, lactose, silica - colloidal anhydrous, magnesium stearate, titanium dioxide, macrogol 6000 and carnauba wax.

### PHARMACOLOGY

#### Pharmacodynamics and Mechanism of Action

Dronedarone is an antiarrhythmic agent with electrophysiological properties of all four Vaughan-Williams classes. It is a multiple ion blocker in animal cardiac tissues *in vitro*, inhibiting potassium currents (including I<sub>K(Ach)</sub>, I<sub>Kur</sub>, I<sub>Kr</sub>, I<sub>Ks</sub> (Class III), sodium currents (Class Ib) and the calcium currents (Class IV). It also non-competitively antagonises adrenergic activity (Class II). In animal models, dronedarone reduces the heart rate. It prolongs Wenckebach cycle length and AH-, PQ-, QT- intervals; with no marked effect or weak increase in on QTc-, HV- and QRS- intervals. It increases effective refractory periods of the atrium, atrio-ventricular node and ventricle with a minimal degree of reverse-use dependency. Dronedarone decreases arterial blood pressure and

myocardial contractility (dP/dt max) with no change in left ventricular ejection fraction and reduces myocardial oxygen consumption. Dronedarone has vasodilatory properties affecting the coronary arteries related to the activation of the nitric oxide pathway. Dronedarone displays indirect antiadrenergic effects; it reduces alpha-adrenergic blood pressure response to epinephrine and beta1 and beta2 responses to isoproterenol.

## Pharmacokinetics

### Absorption

Following oral administration under fed conditions, dronedarone is well absorbed (at least 70%). However due to presystemic first pass metabolism, the absolute bioavailability of dronedarone (given with food) is 15%. Concomitant intake of food increases dronedarone bioavailability by on average 2- to 4-fold. 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 under 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 mean dronedarone C<sub>max</sub> is 84–147 ng/ml and the 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 C<sub>max</sub> 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 (V<sub>ss</sub>) ranges from 1200 to 1400 L.

### Metabolism

Dronedarone is extensively metabolised, mainly by CYP 3A4 (see 'Interactions with Other Medicines'). The major metabolic pathway includes N-debutylation to form the main circulating active metabolite followed by oxidation, oxidative deamination to form the inactive propanoic acid metabolite, followed by oxidation, and direct oxidation. The N-debutyl metabolite exhibits pharmacodynamic activity but is 2 to 10-times less potent than dronedarone.

### Excretion

After oral administration, approximately 6% of the labelled dose is excreted in urine mainly as metabolites (no unchanged compound excreted in urine) and 84% are excreted in faeces mainly as metabolites. After IV administration the plasma clearance of dronedarone ranges from 130 to 150 L/h. The terminal elimination half-life of dronedarone is around 25–30 hours and that of its N-debutyl metabolite around 20–25 hours. In patients, dronedarone and its metabolite are completely eliminated from the plasma within 2 weeks after the end of a 400 mg twice daily-treatment.

### Special Populations

The pharmacokinetics of dronedarone in patients with atrial fibrillation is consistent with that in healthy subjects. The main sources of variability in dronedarone exposure (age, gender, bodyweight, concomitant treatment with weak to moderate CYP 3A4 inhibitors) remain modest in their magnitude (less than 2-fold).

### Gender

In female patients, dronedarone exposures are on average 30% higher as compared to male patients.

### 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 in comparison with patients aged below 65 years.

## Hepatic Impairment

In subjects with moderate hepatic impairment, dronedarone total and unbound exposures are increased by 1.3-fold and by 2-fold respectively. That of the active metabolite are decreased by 1.6-fold to 1.9-fold (see 'DOSAGE AND ADMINISTRATION').

The effect of severe hepatic impairment on the pharmacokinetics of dronedarone has not been assessed (see 'CONTRAINDICATIONS').

## Renal Impairment

Patients with renal impairment were included in clinical studies. Consistent with the very weak renal excretion of dronedarone, no pharmacokinetic modification was observed in patients with renal impairment in particular in patients with severe renal impairment (see 'DOSAGE AND ADMINISTRATION').

## CLINICAL TRIALS

### ATHENA Study

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  $\geq 70$  years old, or  $< 70$  years old with at least one risk factor (including hypertension, diabetes, prior cerebrovascular accident, left atrial diameter  $\geq 50$  mm or LVEF  $< 0.40$ ). The inclusion criteria were later changed such that patients were to be  $\geq 75$  years old, or  $\geq 70$  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. Exclusion criteria included patients with congestive heart failure with NYHA functional class IV, patients with bradycardia ( $< 50$  bpm) and 2<sup>nd</sup> and 3<sup>rd</sup> degree AV block unless treated with a pacemaker. The ATHENA trial also excluded haemodynamically unstable patients and those with permanent AF.

Patients were randomised (4628 patients) and treated for up to 30 months maximum (median follow-up: 22 months) with either MULTAQ 400 mg twice daily (2301 patients) or placebo (2327 patients), on top of standard therapy including beta blockers (71%), ACE inhibitors or angiotensin II receptor antagonists (AIIIRAs) (69%) digitalis (14%), calcium antagonists (14%), statins (39%), oral anticoagulants (60%), aspirin (44%), chronic anti-platelet therapy (6%) and/or diuretics (54%).

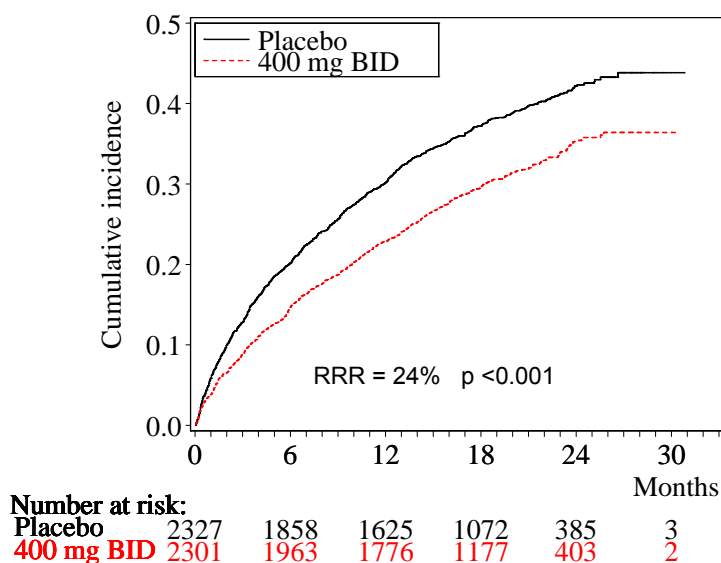
The primary endpoint of the study was the time to first hospitalisation for cardiovascular reasons or death from any cause. Secondary endpoints evaluated were time to death from any cause, time to first hospitalisation for cardiovascular reasons, time to cardiovascular death. In addition, time to sudden death was also assessed. Patients ranged in age from 23 to 97 years and 42% were over 75 years old. Forty seven percent (47%) patients were female and a majority Caucasian (89%).

The majority of patients had hypertension (86%) and structural heart disease (60%) (including Coronary Artery Disease: 30%; Congestive Heart Failure (CHF): 30%; Left ventricular dysfunction  $< 45\%$ : 12%). Twenty five percent (25%) had AF at baseline.

MULTAQ reduced the incidence of cardiovascular hospitalisation or death, from any cause, by a highly significant 24.2% when compared to placebo ( $p < 0.001$ ) with an absolute risk reduction of 7.4% at one year. This difference was entirely attributable to its effect on cardiovascular hospitalisation, principally hospitalisation related to AF and not due to a reduction on all cause mortality.

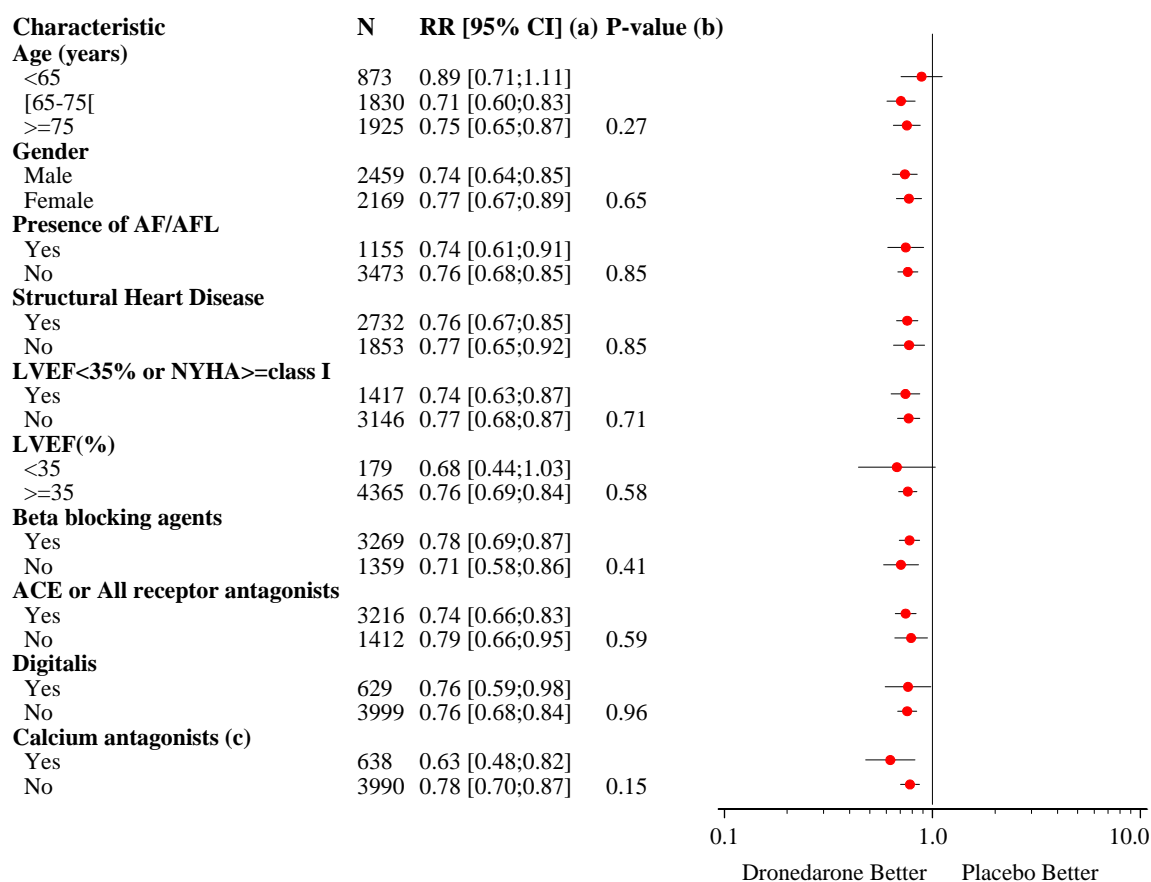
The curves showing the overall event rate are displayed in Figure 1. The event curves separated early and continued to diverge over the 30 month follow-up period.

**Figure 1. Kaplan-Meier cumulative incidence curves from randomisation to first cardiovascular hospitalisation or death from any cause.**



The reduction in cardiovascular hospitalisation or death from any cause was consistent in all subgroups, irrespective of baseline characteristics or medications (ACE inhibitors or AIIIRAs; beta-blockers, digitalis, statins, calcium antagonists, diuretics) (see Figure 2).

**Figure 2. Relative risk (MULTAQ 400 mg twice daily versus placebo) estimates with 95% confidence intervals according to selected baseline characteristics- first cardiovascular hospitalisation or death from any cause**



a Determined from Cox regression model

b P-value of interaction between baseline characteristics and treatment based on Cox regression model

c Calcium antagonists with heart rate lowering effects restricted to diltiazem, verapamil and bepridil

Hospitalisations for major bleeding [0.9% versus 1% (placebo)], syncope [0.9% versus 1% (placebo)] or ventricular arrhythmia (including ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation, and other ventricular arrhythmias) [0.4% versus 0.3% (placebo)] were similar in both groups.

**Table 1: Incidence of Endpoint Events**

	<b>Placebo (N= 2327)</b>	<b>MULTAQ 400mg BID (N= 2301)</b>	<b>HR</b>	<b>95% CI</b>	<b>p-Value</b>
<b>Primary endpoint</b>					
Cardiovascular hospitalization or death from any cause	913 (39.2%)	727 (31.6%)	0.76	[0.68 - 0.83]	<0.0001
<b>Components of the endpoint (as first event)</b>					
• Cardiovascular hospitalization	856 (36.8%)	669 (29.1%)			
• Death from any cause	57 (2.4%)	58 (2.5%)			
<b>Secondary endpoints (any time in study)</b>					
• Death from any cause	135 (5.8%)	115 (5.0%)	0.86	[0.67 - 1.11]	0.24
• Cardiovascular hospitalization	856 (36.8%)	669 (29.1%)	0.74	[0.67 - 0.82]	<0.0001
<b>Components of the cardiovascular hospitalization endpoint (as first event)</b>					
• AF and other supraventricular rhythm disorders	456 (19.6%)	292 (12.7%)	0.61	[0.53 - 0.71]	<0.0001
• Other	400 (17.2%)	377 (16.4%)	0.89	[0.77 -1.03]	0.11

**Table 2** summarises the distribution of deaths across the placebo controlled AF/AFL studies (see section on ANDROMEDA: a study where an increased risk of death in patients with severe heart failure was observed).

Studies	Number of patients with endpoint		Relative Risk [95% CI] (a)
	Placebo	Dronedaron 400mg BID	
DRI3550/DAFNE	0 (N=66)	0 (N=76)	NA
EFC3153/EURIDIS	0 (N=201)	2 (N=411)	NA
EFC4788/ADONIS	5 (N=208)	9 (N=417)	0.794[0.266-2.370]
EFC4508/ERATO	1 (N=89)	1 (N=85)	1.066[0.067-17.046]
EFC5555/ATHENA	139 (N=2311)	116 (N=2293)	0.841[0.657-1.076]
AF/AFL Population	145 (N=2875)	128 (N=3282)	0.849[0.668-1.077]

### EURIDIS, ADONIS, DAFNE, DIONYSOS Studies

In EURIDIS, ADONIS, DAFNE, DIONYSOS studies, the exclusion criteria included patients with congestive heart failure with NYHA functional class III or IV, patients with bradycardia (<50bpm) and 2<sup>nd</sup> and 3<sup>rd</sup> degree AV block unless treated with a pacemaker.

In EURIDIS and ADONIS, a total of 1237 patients with a prior episode of AF or AFL were randomised in an outpatient setting and treated with either MULTAQ 400 mg twice daily (n = 828) or placebo (n = 409) on top of conventional therapies (including oral anticoagulants, beta-blockers, ACE inhibitors or AIIIRAs, chronic antiplatelet agents, diuretics, statins, digitalis, and calcium antagonists). Patients had at least one ECG-documented AF/AFL episode during the last 3 months and were in sinus rhythm for at least one hour and were followed for 12 months.

Patients ranged in age from 20 to 88 years, with the majority being Caucasian (97%), male (69%) patients. The most common co-morbidities were hypertension (56.8%) and structural heart disease (41.5%) including coronary heart disease (21.8%).

In the pooled data from EURIDIS and ADONIS as well as in the individual trials, MULTAQ consistently delayed the time to first recurrence of AF/AFL (primary endpoint). As compared to placebo, MULTAQ lowered the relative risk of first AF/AFL recurrence during the 12-month study period by 25% with an absolute difference in recurrence rate of about 11% at 12 months. The median time from randomisation to first AF/AFL recurrence in the MULTAQ group was 116 days, i.e. 2.2-fold longer than in the placebo group (53 days). The majority (60%) of first recurrences were symptomatic. MULTAQ also delayed the time to symptomatic first recurrence of AF/AFL in both studies. With MULTAQ 400 mg twice daily, the one-year rate of patients with symptomatic first adjudicated recurrence was 37.7%.

In DAFNE where MULTAQ was started before conversion, the median time to AF recurrence, as measured by trans-telephonic electrocardiogram monitoring (TTEM) and 12 lead ECG, was 60 days in the 400 mg twice daily MULTAQ group, compared to 5 days in the placebo group. MULTAQ 400 mg twice daily lowered by 55% (p = 0.001) the risk of first recurrence of AF compared to placebo during the 6 months study period.

The DIONYSOS study compared the efficacy and safety of MULTAQ (400 mg twice daily) versus amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) over 6 months. A total of 504 patients with documented AF were randomised, 249 received dronedarone and 255 received amiodarone. The incidence of the primary efficacy endpoint defined as first recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy at 12 months was 75% in the MULTAQ group and 59% in the amiodarone group (hazard ratio=1.59, log-rank p-value <0.0001). AF recurrence was 63.5% versus 42%, respectively. Recurrences of AF (including

absence of conversion) were more frequent in the dronedarone group, whereas premature study drug discontinuations due to intolerance were more frequent in the amiodarone group.

The incidence of the main safety endpoint defined as the occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye or gastrointestinal specific events or premature study drug discontinuation following any adverse event was reduced by 20% in the dronedarone group compared to the amiodarone group ( $p=0.129$ ). This reduction was driven by the occurrence of significantly fewer thyroid and neurological events and a trend for less skin or ocular events, and fewer premature study drug discontinuations compared to the amiodarone group.

More gastrointestinal adverse events, mainly diarrhoea, were observed in the dronedarone group (12.9% versus 5.1%).

### **ERATO Study**

In the ERATO study, a double-blind, placebo-controlled 6-month clinical trial, 174 patients with symptomatic permanent (lasting over 6 months) AF were randomised and treated with either MULTAQ 400 mg twice daily (85 patients) or placebo (89 patients), in addition to conventional therapy. Exclusion criteria included patients with congestive heart failure with NYHA functional class III or IV, patients with bradycardia ( $<50$ bpm) and 2<sup>nd</sup> and 3<sup>rd</sup> degree AV block unless treated with a pacemaker. Patients ranged in age from 31 to 86 years, with the majority being Caucasian (99%), male (69%) patients. The most common co-morbidities were hypertension (49%) and structural heart disease (39%). At day 14, MULTAQ decreased mean ventricular rate as compared to placebo. This effect was independent of background rate control therapies and maintained for 4 months after treatment initiation with a mean decrease from baseline equal to 8.8 bpm ( $p < 0.0001$ ). A decrease of ventricular rate was also observed during maximal exercise at day 14 ( $-24.5$  bpm,  $p < 0.0001$ ). There was no difference in duration of maximal exercise.

In the pooled data from EURIDIS and ADONIS, patients treated with MULTAQ 400 mg twice daily had lower mean ventricular rates at the time of first recurrence (103.4 bpm) as compared to placebo patients (117.1 bpm) (TTEM method,  $p < 0.0001$ ).

### **ANDROMEDA Study (Increased Mortality in Patients with Severe Heart Failure)**

ANDROMEDA, a study performed in 627 patients recently hospitalised with symptomatic heart failure and severe left ventricular dysfunction (wall motion index  $\leq 1.2$ ) was stopped prematurely due to an excess of deaths in the MULTAQ group. Twenty-five (25) patients in the dronedarone group (8.1%) versus 12 patients in the placebo group (3.8%) had died, hazard ratio 2.13; 95% CI: 1.07 to 4.25;  $p=0.027$ . The main reason for death was worsening heart failure. There were also excess hospitalisations for cardiovascular reasons in the dronedarone group (71 versus 50 for placebo) (see 'CONTRAINDICATIONS').

The populations enrolled in the ANDROMEDA and ATHENA studies were significantly different. The patients enrolled in ANDROMEDA had relatively severe heart failure and had been hospitalised, or referred to a specialty heart failure clinic, for worsening symptoms of heart failure, notably shortness of breath. Note that these patients may have been clinically improved at the time of enrolment and it is the history of decompensation that characterised them. Patients enrolled into ANDROMEDA were predominantly NYHA functional class II (40%) and III (57%), and only 38% had a history of AF/AFL (25% had AF at randomisation). In contrast, in ATHENA, 71% of patients had no heart failure, 25% were NYHA functional class I or II, and only 4% were functional class III. All patients had a history of AF/AFL.

### **INDICATIONS**

To reduce the risk of cardiovascular hospitalisation in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors, who are in sinus rhythm or who will be cardioverted, on top of standard therapy (see 'CLINICAL TRIALS').

## CONTRAINDICATIONS

Combined therapy with medicines which may induce torsades de pointes such as phenothiazines, cisapride, tricyclic antidepressants, certain oral macrolides, Class I and III antiarrhythmics and drugs that prolong the QT interval (see 'Interactions with other Medicines').

Hypersensitivity to dronedarone or to any of the excipients.

Second- or third- degree AV block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker).

Bradycardia < 50 bpm.

Patients with NYHA Class IV heart failure or NYHA Class II - III heart failure with recent decompensation requiring hospitalisation (see Boxed Warning).

Co-administration with strong CYP 3A4 inhibitors such as ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir, clarithromycin, cyclosporin, (see 'Interactions with other Medicines').

QTc Bazett interval  $\geq$  500 msec.

Severe hepatic impairment.

Pregnancy and/or lactation (see 'PRECAUTIONS, Use in Pregnancy and Lactation').

Severe renal impairment (CrCl <30ml/min).

## PRECAUTIONS

### Heart failure assessment

MULTAQ must not be initiated in patients with NYHA Class IV heart failure or Class II-III heart failure with recent decompensation requiring hospitalisation (see 'CONTRAINDICATIONS and Boxed Warning').

Assess AF/AFL patients for the cause, severity and stability of heart failure to identify appropriate patients for the initiation of treatment with MULTAQ.

This assessment should include:

- A physical examination
- An assessment of the patient's current NYHA heart failure classification
- Other assessments (e.g. ECG, chest X-rays, lab tests, ECHO) may be appropriate depending on severity and prognosis
- An assessment of heart failure stability including identification of recent decompensation

Periodic assessment for signs or symptoms of heart failure should be performed (see precaution "Patients with New or Worsening Heart Failure during Treatment" below).

### New York Heart Association (NYHA) grading system for severity of heart failure symptoms

NYHA Grading	Symptoms
Class I Asymptomatic	No limitations in normal physical activity
Class II Mild	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris
Class III Moderate	Marked limitation of physical activity. Less than ordinary activity results in symptoms
Class IV Severe	Unable to carry out any physical activity without discomfort. Symptoms present at rest

## **Patients with New or Worsening Heart Failure during Treatment**

Periodic assessment for signs or symptoms of heart failure should be performed. Patients should be advised to consult a physician if they develop signs or symptoms of heart failure, such as weight gain, dependent oedema, or increasing shortness of breath. There are limited data available for AF/AFL patients who develop worsening heart failure during treatment with MULTAQ. If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ.

### **Management of serum creatinine increase**

It is recommended to measure serum creatinine values prior to and 7 days after initiation of MULTAQ. If an increase in serum creatinine is observed, this value should be used as the new reference baseline taking into account that this may be expected with MULTAQ.

An increase in plasma creatinine has been observed with MULTAQ 400 mg twice daily in healthy subjects and in patients. This increase occurs early after treatment initiation and reaches a plateau after 7 days. An increase in serum creatinine should not necessarily lead to the discontinuation of treatment with ACE-inhibitors or Angiotensin II Receptor Antagonists (AIIIRAs). Mean increase in AF or AFL patients is about 10 µmol/L. Values return to baseline within one week after treatment discontinuation. In a specific study in healthy subjects, this increase was shown to be related to inhibition of creatinine secretion at the tubular level, with no effect on glomerular filtration or on renal blood flow.

### **Management of liver enzyme increase**

It is recommended to measure liver enzymes at commencement of treatment and thereafter when clinically indicated. Elevations of liver enzymes (e.g. AST, ALT) have occurred during dronedarone studies (2.5% dronedarone vs 2% placebo). These elevations were generally asymptomatic. The incidence of hepatic disorders reported was 2.9% with dronedarone vs 2.5% with placebo. However, if an increase in AST or ALT of > 3X ULN is observed, and no other cause is found, consideration should be given to withdrawal of MULTAQ therapy.

### **Patients with renal impairment**

MULTAQ is contraindicated in patients with CrCl <30ml/min (see CONTRAINDICATIONS).

### **Patients with severe hepatic impairment.**

Multaq is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS).

### **Electrolytes imbalance**

Since antiarrhythmic medicinal products may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before initiation and during MULTAQ therapy.

### **QT prolongation**

The pharmacological action of MULTAQ may induce a moderate (average of about 10 msec but much greater effects have been observed) QTc Bazett prolongation, related to prolonged repolarisation. Follow up, including ECG, is recommended during treatment. If QTc Bazett interval is ≥ 500 msec, MULTAQ should be stopped (see 'CONTRAINDICATIONS'). Based on clinical experience, MULTAQ has a low pro-arrhythmic effect. However, proarrhythmic effects may occur in particular situations such as concomitant use with drugs favouring arrhythmia and/or electrolytic disorders (see 'Interactions with other Medicines').

### **Bradycardia**

Multaq has been associated with an increased risk of bradycardia compared with placebo (3.3% vs 1.3% on placebo) (see CONTRAINDICATIONS).

### **Patients with galactose intolerance**

Due to the presence of lactose in the excipients, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take MULTAQ.

## **Carcinogenicity and Mutagenicity**

**Genotoxicity** Dronedarone was negative in tests for bacterial gene mutation, hepatocyte DNA repair, lymphocyte chromosomal aberration *in vitro*, *in vivo* mouse micronucleus test for clastogenicity. Equivocal results were obtained in a mammalian cell gene mutation assay. The weight of evidence based on all the genotoxicity assays suggests dronedarone is unlikely to pose a genotoxic risk in patients.

**Carcinogenicity:** Long term carcinogenicity studies have been conducted in mice and rats. Dronedarone treatment resulted in an increased incidence of mammary gland adenocarcinomas in female mice, at the highest tested dose (300 mg/kg/day) resulting in drug exposure (based on AUC) approximately 8 times the human value with the recommended dose (400 mg BID). A mechanistic study suggested that this was probably related to elevated prolactin. An increased incidence of histiocytic sarcomas was also observed in male mice at the same dronedarone dose. In rats, there was an increased incidence of mesenteric lymph node haemangiomas in males and females at the highest tested dose (70 mg/kg/day) resulting in a drug exposure (based on AUC) approximately 5 times the human value. The relevance of these findings to humans is uncertain.

## **Impairment of Fertility**

In fertility studies in rats, an increase in oestrous cycle length and females with irregular oestrous cycles or acyclic occurred at  $\geq 30$ mg/kg/day. Corpora lutea and implantations were decreased and resorptions increased at 100mg/kg/day. The drug exposure (based on AUC) at 30mg/kg/day was below the human value with the recommended dose (400mg BID). The number of animals with testicular atrophy, tubular mineralisation and aspermia and epididymal changes were increased in rats dosed with 70mg/kg/day (5 times the clinical exposure) for 2 years, but no testicular effects were observed in rats at 50mg/kg/day (2 times the clinical exposure) for 6 months, in mice at 300mg/kg/day (8 times the clinical exposure) for 2 years and in dogs at up to 45mg/kg/day (15 times the clinical exposure) for one year. Relevance of the testicular and epididymal findings to humans is uncertain.

## **Use in Pregnancy**

Category D

MULTAQ is contraindicated in pregnant women (see 'CONTRAINDICATIONS'). Women of childbearing potential should use effective methods of contraception during treatment with MULTAQ.

There are no adequate data from the use of dronedarone in pregnant women. Dronedarone was teratogenic in rats, and induced multiple external, visceral and skeletal malformations at  $\geq 80$  mg/kg/day (exposure based on AUC slightly greater than 2 times the clinical value at 400 mg BID). There was no evidence of teratogenicity in rabbits at up to 60 mg/kg/day (below the clinical exposure based on AUC).

## **Use in Lactation**

It is not known whether dronedarone is excreted in human breast milk. Animal studies have shown excretion of dronedarone and its metabolites in breast milk. Woman should not breast-feed while taking MULTAQ (see 'CONTRAINDICATIONS').

## **Use in Elderly**

A large number of elderly patients with AF/AFL have been included in the MULTAQ clinical program (more than 4500 patients aged 65 years of age or above, of which more than 2000 patients were 75 years or above). Efficacy and safety was comparable in both elderly and younger patients (see DOSAGE AND ADMINISTRATION).

## **Paediatric Use**

There is no experience in children and adolescents.

## **Effects on Ability to Drive and Use Machinery**

No studies on the effects on the ability to drive and use machines have been performed.

## Interactions with Other Medicines

Dronedarone is primarily metabolised by CYP 3A4 (see 'Pharmacokinetics'). Dronedarone and the N-debutyl metabolite are moderate inhibitors of CYP 3A4 and mild inhibitors of CYP 2D6.

Therefore, inhibitors and inducers of CYP 3A4 have the potential to interact on dronedarone, and dronedarone has the potential to interact on medicinal products substrates of CYP 3A4 and CYP 2D6. It is a potent inhibitor of P-glycoproteins (P-gp). Dronedarone therefore, has the potential to interact on medicinal products substrates of P-glycoproteins. Dronedarone has no significant potential to inhibit CYP 1A2, CYP 2C9, CYP 2C19, CYP 2C8 and CYP 2B6.

A potential pharmacodynamic interaction can also be expected with beta-blockers, calcium antagonists and digitalis.

In clinical trials, patients treated with dronedarone received a variety of concomitant medications including beta-blockers, digitalis, calcium antagonists (including those with heart rate-lowering effects), statins and oral anticoagulants.

### Pharmacodynamic Interactions

#### *Drugs prolonging the QT interval (inducing Torsade de Pointes)*

Medicinal products inducing torsades de pointes such as phenothiazines, cisapride, tricyclic antidepressants, certain oral macrolides and Class I and III antiarrhythmics are contraindicated because of the potential risk of proarrhythmia (see 'CONTRAINDICATIONS'). Caution should also be taken with co-administration with beta-blockers or digoxin.

#### *Digoxin*

Digoxin can potentiate the electrophysiologic effects of dronedarone (such as decreased AV-node conduction). In clinical trials, increased levels of digoxin were observed when dronedarone was co-administered with digoxin. Gastrointestinal disorders were also increased.

Because of the pharmacokinetic interaction and possible pharmacodynamic interaction, reconsider the need for digoxin therapy. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely and clinical and ECG monitoring is recommended.,

#### *Calcium channel blockers*

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

Repeated doses of diltiazem (240 mg twice daily), verapamil (240 mg once daily) and nifedipine (20 mg twice daily) resulted in an increase in dronedarone exposure of 1.7-, 1.4-, and 1.2- fold, respectively. Calcium antagonists also have their exposure increased by dronedarone (400 mg twice daily) (verapamil by 1.4- fold, and nisoldipine by 1.5- fold). In clinical trials, there was no evidence of safety concerns when dronedarone was co-administered with calcium antagonists with heart rate-lowering effects.

Overall, due to the pharmacokinetic interaction and possible pharmacodynamic interaction, calcium antagonists with depressant effects on sinus and atrio-ventricular node such as verapamil and diltiazem should be used with caution when associated with dronedarone.

These drugs should be initiated at low dose and up-titration should be done only after ECG assessment. In patients already on calcium antagonists at time of dronedarone initiation, an ECG should be performed and the dose should be adjusted if needed.

#### *Beta-blockers*

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

Give low dose of beta-blockers initially, and increase only after ECG verification of good tolerability. In patients already on beta-blockers at time of dronedarone initiation, an ECG should be performed and the beta-blocker dose should be adjusted if needed.

## Effects of Other Drugs on Dronedarone

### *Ketoconazole and other potent CYP 3A inhibitors*

Repeated doses of 200mg daily ketoconazole, a strong CYP 3A inhibitor, resulted in a 17-fold increase in dronedarone exposure and a 9-fold increase in  $C_{max}$ . Concomitant use of ketoconazole as well as other potent CYP 3A inhibitors such as itraconazole, voriconazole, posaconazole, ritonavir, clarythromycin, and cyclosporin is contraindicated (see CONTRAINDICATIONS).

Other moderate inhibitors of the CYP3A4 such as erythromycin are also likely to increase dronedarone exposure.

### *Grapefruit juice*

Grapefruit juice, a moderate inhibitor of CYP 3A, resulted in a 3-fold increase in dronedarone exposure and a 2.5-fold increase in  $C_{max}$ . Therefore, patients should avoid grapefruit juice beverages while taking Multaq.

### *Calcium channel blockers*

Verapamil and diltiazem are moderate CYP 3A inhibitors and increase dronedarone exposure by approximately 1.4-to 1.7-fold.

### *Rifampin and other CYP 3A inducers*

Rifampin decreased dronedarone exposure by 80%. Avoid rifampin or other CYP 3A inducers such as phenobarbital, carbamazepine, phenytoin, and St John's Wort with dronedarone because they decrease its exposure significantly.

### *Pantoprazole*

Pantoprazole (40mg once daily), a drug that increases gastric pH, did not have a significant effect on dronedarone pharmacokinetics.

## Effects of Dronedarone on Other Drugs

### *Statins*

Dronedarone can increase exposure of statins that are substrates of CYP 3A4 and/or P-gp substrates. Dronedarone (400 mg twice daily) increased simvastatin and simvastatin acid exposure by 4- fold and 2- fold respectively. It is predicted that dronedarone could also increase the exposures of lovastatin and atorvastatin within the same range as simvastatin acid. Interaction of dronedarone on statins transported by OATP, such as fluvastatin and rosuvastatin has not been studied. In clinical trials, there was no evidence of safety concerns when dronedarone was co-administered with statins metabolized by CYP 3A4.

As high doses of statins increase the risk of myopathy, concomitant use of statins should be undertaken with caution. Lower starting dose and maintenance doses of statins should be considered according to the statin Product Information recommendations and patients monitored for clinical signs of muscular toxicity.

### *Calcium channel blockers*

Dronedarone increases calcium channel blocker (verapamil, diltiazem or nifedipine) exposure by 1.4- to 1.5-fold.

### *Sirolimus, tacrolimus, and other CYP3A substrates with narrow therapeutic range*

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

### *Beta-blockers and other CYP 2D6 substrates*

Dronedarone increased propranolol exposure by approximately 1.3-fold following single dose administration. Dronedarone increased metoprolol exposure by 1.6-fold following multiple dose administration. Other CYP 2D6 substrates, including other beta-blockers, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) may have increased exposure upon co-administration with dronedarone.

#### *Digoxin and P-glycoprotein substrates*

Dronedarone increased digoxin exposure by 2.5-fold by inhibiting the P-gP transporter. Dronedarone inhibits P-gP and interactions may therefore occur with doxorubicin and fexofenadine. Other P-gP substrates are expected to have increased exposure when coadministered with dronedarone.

#### *Warfarin and losartan (CYP 2C9 substrates)*

In healthy subjects, dronedarone at a dose of 600 mg twice daily increased S-warfarin exposure by 1.2-fold with no change in R-warfarin and with no clinically significant increase in INR. In clinical trials in patients with AF/AFL, there was no observed excess risk of bleeding compared to placebo when dronedarone was co-administered with oral anticoagulants. Monitor INR per the warfarin label.

No interaction was observed between dronedarone and losartan.

#### *Theophylline (CYP 1A2 substrate)*

Dronedarone 400 mg twice daily does not increase the steady state theophylline exposure.

#### *Oral contraceptives*

No decreases in ethinylestradiol and levonorgestrel concentrations were observed in healthy subjects receiving dronedarone concomitantly with oral contraceptives. Ethinylestradiol and levonorgestrel exposure were increased.

### **ADVERSE EFFECTS**

The safety profile of MULTAQ 400 mg twice daily in patients with AF or AFL is based on 5 placebo controlled studies, ATHENA, EURIDIS, ADONIS, ERATO and DAFNE. In these studies, a total of 6285 patients were randomized and treated. Of these, 3282 patients were treated with dronedarone 400 mg twice daily, and 2875 received placebo.

The mean exposure across studies was 13 months. In ATHENA, the maximum follow-up was 30 months. Assessment of intrinsic factors such as race, gender or age on the incidence of any treatment emergent adverse events did not suggest any excess of adverse events in a particular sub-group.

In clinical trials, premature discontinuation due to adverse reactions occurred in 11.8% of the dronedarone-treated patients and in 7.7% in the placebo-treated group. The most common reasons for discontinuation of therapy with MULTAQ were gastrointestinal disorders (3.2 % of patients versus 1.8% in the placebo group) and QT prolongation (1.1 % of patients versus 0.4% in the placebo group).

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

Table 3 lists adverse events reported in > 2% of dronedarone treated patients and at an incidence higher than in the placebo group in the 5 placebo controlled AF/AFL trials. Adverse events are shown *whether or not categorized as "possibly drug related"*.

**Table 3 - Number % of patients with Adverse Events with an incidence >2% in dronedarone treatment group and at an incidence higher than placebo presented by system organ class**

	<b>Placebo N=2875</b>	<b>Dronedarone 400 mg BID N=3282</b>
<b>Gastrointestinal disorders</b>		
Diarrhoea*	5.8%	9.0%
Nausea*	3.1%	4.9%
Abdominal pain (including upper and lower)*	2.8%	3.5%
Vomiting*	1.1%	2.0%
<b>Infections and infestations</b>		
Urinary tract infection	2.3%	2.7%
<b>General disorders and administration site conditions</b>		
Oedema peripheral	4.9%	5.8%
Fatigue*	3.6%	4.3%
Asthenia*	1.7%	2.3%
<b>Nervous system disorders</b>		
Dizziness	5.6%	5.8%
<b>Musculoskeletal and connective tissue disorders</b>		
Back pain	3.1%	3.2%
Pain in extremity	1.7%	2.2%
Arthralgia	2.4%	2.7%
<b>Respiratory, thoracic and mediastinal disorders</b>		
Dyspnoea	4.0%	4.5%
<b>Investigations</b>		
Blood creatinine increased*	1.1%	4.0%
<b>Cardiac disorders</b>		
Bradycardia*	1.3%	3.3%
<b>Skin and subcutaneous tissue disorders</b>		
Rash (including generalized, macular, maculo-papular)*	1.6%	2.7%

\* Adverse events considered as related to dronedarone

In addition, the following adverse drug reactions (possibly drug related) were reported at an incidence less than 2 % in patients treated with MULTAQ.

The following CIOMS frequency rating is used, when applicable:

Very common  $\geq 10$  %; Common  $\geq 1$  and  $< 10$  %; Uncommon  $\geq 0.1$  and  $< 1$  %; Rare  $\geq 0.01$  and  $< 0.1$  %; Very rare  $< 0.01$  %.

#### **Gastrointestinal disorders**

Common: dyspepsia,

#### **Nervous system disorders**

Uncommon: dysgeusia,

Rare: ageusia,

#### **Skin and subcutaneous tissue disorders**

Common: pruritus,

Uncommon: erythemas (including erythema and rash erythematous), eczema, photosensitivity reactions, dermatitis & dermatitis allergic

The following laboratory data/ECG parameters were also reported with MULTAQ 400 mg twice daily.

**Table 3: ECG parameters/ Laboratory data**

	<b>Placebo (N=2875)</b>	<b>MULTAQ 400 mg twice daily (N=3282)</b>
QTc Bazett prolonged** (> 450 msec in male > 470 msec in female)	18.7% (419/2237)	27.6%(746/2707)
QTc Bazett ** Increase in [30 - 60] ms versus baseline	26.5 % (519 /1960)	36.6 % (846 /2312)
QTc Bazett ** Increase > 60 ms versus baseline	8.8 % (173 /1960)	15.6 % (361 /2312)
QTc Bazett >=500 ms	3.9 % (87 /2237)	6.4 % (174 /2707)
ALT (SGPT-ALAT)*** > 2 ULN	6.1% (34/559)	5.8% (57/979)
> 3 ULN	2.0%(11/559)	2.5% (24/979)
> 5 ULN	0.9% (5/559)	0.8% (8/979)
AST (SGOT-ASAT)*** > 2 ULN	2.9% (16/558)	2.5% (24/979)
> 3 ULN	1.1% (6/558)	1.0% (10/979)
> 5 ULN	0.0% (0/558)	0.5% (5/979)
Blood creatinine increased ≥ 10% five days after treatment initiation	20.6% (533/2875)	50.9% (1670/3282)

\*\* Patients with missing baseline assessment are not taken into account.

\*\*\*not measured in ATHENA study

## **DOSAGE AND ADMINISTRATION**

### **Adults**

The only recommended dose is 400 mg twice daily, taken as one tablet with the morning meal and one tablet with the evening meal. Grapefruit juice should not be taken together with MULTAQ (see Interactions with other medicines).

Doses above 400 mg are not more effective and are less well tolerated.

Treatment with Class I or III antiarrhythmics (such as flecainide, quinidine, disopyramide, sotalol, amiodarone) or drugs that are strong inhibitors of CYP3A (e.g. ketoconazole) must be stopped before starting MULTAQ (see 'CONTRAINDICATIONS').

Treatment with MULTAQ can be initiated in an outpatient setting.

### **Elderly**

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). Although dronedarone exposure was increased in a pharmacokinetic study conducted in healthy subjects, dose adjustments are not considered necessary (see 'PRECAUTIONS, Pharmacology, Special Populations').

### **Children**

There is no experience in children and adolescents. Multaq is not recommended in these patients.

**Hepatic impairment**

No dosage adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2). MULTAQ is contraindicated in patients with severe hepatic impairment because of the absence of data (see 'CONTRAINDICATIONS').

**Renal impairment**

MULTAQ is contraindicated in patients with severe renal impairment (creatinine clearance (CrCl) <30ml/min) (see CONTRAINDICATIONS). No dosage adjustment is required in other patients with renal impairment (see 'PHARMACOLOGY, Pharmacokinetics').

**OVERDOSAGE**

It is not known whether MULTAQ and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). There is no specific antidote available. In the event of overdose, treatment should be supportive and directed toward alleviating symptoms. Contact the Poisons Information Centre for advice on management of overdose.

**PRESENTATION AND STORAGE CONDITIONS**

White, oblong shaped, film-coated tablets engraved with a double wave marking on one side and "4142" code on the other side.

The tablets are supplied in blisters in packs of 20, 50, 60 and 100 tablets and in bottles of 60, 180 & 500 tablets.

Store below 30°C.

**NAME AND ADDRESS OF THE SPONSOR**

sanofi-aventis australia pty ltd  
12-24 Talavera Road  
Macquarie Park, NSW 2113

**POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine (Schedule 4)

**DATE OF TGA APPROVAL:**

19<sup>th</sup> July 2010