PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr MULTAQ®

Dronedarone Tablets

400 mg dronedarone (as dronedarone hydrochloride)

For oral use

Antiarrhythmic Agent

ATC code: C01BD07

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	2024-10

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Sections or subsections that are not applicable at the time of authorisation are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MULTAQ (dronedarone hydrochloride) is indicated for:

- the treatment of patients with paroxysmal or persistent atrial fibrillation (AF) who are in sinus rhythm or who are intended to be cardioverted, to reduce the risk of cardiovascular hospitalization due to atrial fibrillation (see 14 CLINICAL TRIALS). MULTAQ should only be prescribed after alternative treatment options have been considered.

1.1 Pediatrics

- Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

- Efficacy and safety were comparable in both elderly and younger patients. Caution is needed in elderly patients ≥ 75 years with multiple co morbidities.

2 CONTRAINDICATIONS

MULTAQ is contraindicated in patients with:

- Permanent atrial fibrillation of any duration in which sinus rhythm cannot be restored and attempts to restore it are no longer considered by the attending physician.
- History of, or current heart failure, regardless of NYHA functional class
- Left ventricular systolic dysfunction
- Second- or third- degree atrio-ventricular (AV) block, complete bundle branch block, distal block, sinus node dysfunction, atrial conduction defects or sick sinus syndrome, (except when used in conjunction with a functioning pacemaker)
- Unstable hemodynamic condition(s)
- Bradycardia < 50 bpm
- Patients with liver or lung toxicity related to the previous use of amiodarone
- Co-administration with strong CYP3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporin, clarithromycin, and ritonavir (see 9 DRUG INTERACTIONS)
- Co-administration with drugs inducing torsades de pointes such as phenothiazines, tricyclic antidepressants, and certain oral macrolides, class I and III antiarrhythmics
- QTc Bazett interval ≥ 500 msec
- Severe hepatic impairment
- Pregnancy (see 7.1 WARNINGS AND PRECAUTIONS, Special Populations)
- Lactation (see 7.1 WARNINGS AND PRECAUTIONS, Special Populations)
- History of hypersensitivity reactions to dronedarone or any of its excipients or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing considerations

There is limited information on the optimal timing to switch from amiodarone to MULTAQ. It should be considered that amiodarone may have a long duration of action after discontinuation due to its long half-life. If a switch is considered, this should be done with caution under the supervision of a specialist.

Treatment with class I or III antiarrhythmics (such as flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol, amiodarone) must be stopped before starting MULTAQ.

4.2 Recommended Dose and Dosage Adjustment

- The recommended dosage is 400 mg twice daily in adults. MULTAQ should be taken as one tablet with the morning meal and one tablet with the evening meal.
- Treatment with MULTAQ can be initiated in an outpatient setting.

Renal Impairment

- No dose adjustment is required in patients with renal impairment (see 7.1 WARNINGS AND PRECAUTIONS, Special Populations and 10.3 Pharmacokinetics).

Severe Hepatic impairment

- MULTAQ is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS).

4.5 Missed Dose

If a dose of this medication has been missed, the missed dose should be skipped and the patient should go back to the regular dosing schedule. The dose should not be doubled.

5 OVERDOSE

In the event of overdosage, the patient's cardiac rhythm and blood pressure should be monitored in addition to general supportive measures. Treatment should be supportive and based on symptoms.

It is not known whether dronedarone and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis or hemofiltration). There is no specific antidote available.

For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	tablet 400 mg	carnauba wax, colloidal anhydrous silica,

		crospovidone, hypromellose, lactose monohydrate, macrogol 6000, magnesium stearate, maize starch, poloxamer 407, titanium dioxide.

Description

MULTAQ is provided as tablets for oral administration.

Each tablet of MULTAQ contains dronedarone hydrochloride equivalent to 400 mg dronedarone".

The inactive ingredients are:

Core of the tablets: colloidal anhydrous silica, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, maize starch, poloxamer 407.

Coating / Polishing of the tablets: carnauba wax, hypromellose, macrogol 6000, titanium dioxide.

6.1 Physical Characteristics

MULTAQ 400 mg tablets are provided as white film-coated tablets for oral administration, oblong-shaped, engraved with a double wave marking on one side and "4142" code on the other side in: bottles of 60 tablets, 180 tablets, 500 tablets, and in boxes of 4 blisters (15 tablets per blister).

7 WARNINGS AND PRECAUTIONS

General

Anticoagulation Therapy

Patients should be appropriately anticoagulated. Where applicable, International Normalized Ratio (INR) should be closely monitored after initiating dronedarone in patients taking vitamin K antagonists as per their label.

Dronedarone should not be used concomitantly with either dabigatran or rivaroxaban since it may increase exposure of dabigatran through P-gp inhibition or rivaroxaban through P-gp and CYP3A4 inhibition (see 9 DRUG INTERACTIONS).

Cardiovascular

Congestive Heart Failure (CHF) or Left Ventricular Systolic Dysfunction

Dronedarone is contraindicated for use in patients in unstable hemodynamic conditions, history of, or current heart failure or left ventricular systolic dysfunction. (see 2 CONTRAINDICATIONS).

Patients with new or worsening heart failure during treatment

Patients should be advised to consult a physician if they develop signs or symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath. If heart failure develops treatment with MULTAQ should be discontinued (see 2 CONTRAINDICATIONS).

Patients should be followed for the development of left ventricular systolic dysfunction during treatment. If left ventricular systolic dysfunction develops, treatment with MULTAQ should be discontinued.

Patients Developing Permanent AF During Treatment

A clinical study in patients with permanent AF (AF duration for at least 6 months) and cardiovascular risk factors was stopped early due to an excess of cardiovascular death, stroke and unplanned cardiovascular hospitalization. It is recommended to perform an ECG at least every 6 months while patients are receiving MULTAQ. If patients treated with MULTAQ develop permanent AF, treatment with MULTAQ should be discontinued.

Patients with Coronary Artery Disease

Caution is needed in patients with coronary artery disease.

QT prolongation

The pharmacological action of dronedarone may induce a moderate (about 10 msec) QTc Bazett prolongation, related to prolonged repolarization. These changes are linked to the therapeutic effect of dronedarone and do not reflect toxicity. Follow up, including ECG, is recommended during treatment. If QTc Bazett interval is ≥ 500 msec, dronedarone should be stopped (see 2 CONTRAINDICATIONS).

Based on clinical experience, dronedarone has a low pro-arrhythmic effect. However, proarrhythmic effects may occur in particular situations such as concomitant use with drugs favoring arrhythmia and/or electrolytic disorders (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

Endocrine and Metabolism

Electrolyte imbalance

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

Hepatic/Biliary/Pancreatic

Liver Injury

Hepatocellular liver injury, including acute liver failure requiring transplant, has been reported in patients treated with MULTAQ in the post-marketing setting. Healthcare professionals should advise patients treated with MULTAQ to immediately report symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching). It is not known whether routine periodic monitoring of serum enzymes will detect the development of severe liver injury. However, healthcare professionals should consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment. If hepatic injury is suspected, MULTAQ should be discontinued immediately followed by appropriate blood tests. If liver injury is found, appropriate treatment should be instituted, and investigations should be performed to establish the cause. The safety of restarting MULTAQ in patients who have sustained liver injury from any cause is unknown; accordingly, its use in such patients is not recommended.

Monitoring and Laboratory Tests

It is recommended to closely monitor patients taking MULTAQ including ECG at least every 6 months. If patients treated with MULTAQ develop permanent AF, treatment with MULTAQ should be discontinued.

Management of plasma creatinine increase

It is recommended that baseline values of plasma creatinine be established 7 days after initiation of treatment with dronedarone.
If the result obtained for the plasma creatinine is above the upper limit of normal as provided by the laboratory, this value should be used as the new reference baseline taking into account that this may be expected with dronedarone, since the drug can affect baseline values. An increase in creatinemia should not necessarily lead to the discontinuation of treatment with dronedarone or discontinuation of treatment with ACE-inhibitors or angiotensin receptor blockers (ARBs) (see 7 WARNINGS AND PRECAUTIONS, Renal).

Liver function testing
Healthcare professionals should advise patients treated with MULTAQ to immediately report symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching). It is not known whether routine periodic monitoring of serum enzymes will detect the development of severe liver injury. However, healthcare professionals should consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment. If hepatic injury is suspected, MULTAQ should be discontinued immediately followed by appropriate blood tests. If liver injury is found, appropriate treatment should be instituted, and investigations should be performed to establish the cause. The safety of restarting MULTAQ in patients who have sustained liver injury from any cause is unknown; accordingly, its use in such patients is not recommended.
Further laboratory testing is at the discretion of the attending physician.

Renal

Plasma Creatinine Increase
An increase in plasma creatinine has been observed with dronedarone 400 mg twice daily in healthy subjects and in patients. This increase occurs early after treatment initiation and reaches a plateau after 7 days. Mean increase in patients with atrial fibrillation 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. The same mechanism has also been described with other drugs such as cimetidine, trimethoprime or amiodarone. Increased plasma creatinine could be misinterpreted and lead to inappropriate discontinuation of ACE inhibitors or AIIRAs in patients requiring this treatment (see 7 WARNINGS AND PRECAUTIONS).

Larger increases in creatinine after dronedarone initiation have been reported in the post-marketing setting. Some cases also reported increases in blood urea nitrogen, possibly due to hypoperfusion secondary to developing CHF (pre-renal azotaemia). In such cases, dronedarone should be stopped. It is recommended to monitor renal function periodically and to consider further investigations as needed (see 8.5 Post-Market Adverse Drug Reactions, Renal).

Renal impairment
Patients with renal impairment were included in clinical studies. Consistent with the minimal renal excretion of dronedarone, no pharmacokinetic modification was observed in patients with renal impairment in particular in patients with severe renal impairment though patients with severe renal impairment were present only in small numbers in these studies. From a clinical standpoint, limited experience is available in patients with severe renal impairment (see 8.5 Post-Market Adverse Drug Reactions, Renal).

Reproductive Health

MULTAQ is contraindicated in women who are or may become pregnant (see 2 CONTRAINDICTIONS, 7.1.1 Special Populations, Pregnant Women and 16 NON-CLINICAL TOXICOLOGY)

- Teratogenic Risk

  MULTAQ has been shown to be teratogenic in the rat.

Respiratory

Cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported in post-marketing experience (see 8.5 Post-Market Adverse Drug Reactions). Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity and patients should be carefully evaluated clinically. If pulmonary toxicity is confirmed treatment should be discontinued.

7.1 Special Populations

7.1.1 Pregnant Women

Contraception
Women of childbearing potential should use effective methods of contraception during treatment with MULTAQ and for 7 days after the final dose. 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.

MULTAQ can cause fetal harm when administered to pregnant women. In rats, dronedarone caused marked effects on embryo-fetal development at 100 mg/kg/day such as increased post-implantation losses, reduced fetal and placental weights and various external, visceral and skeletal malformations in most fetuses. At lower dosages, up to 50 mg/kg/day (corresponding to 4.5 times the recommended human therapeutic dose), dronedarone had no effects on the litters (with the exception of a transient minor effect on the bodyweight gain of the pups from D1 to D4 post-partum). Dronedarone had no adverse effects on the mothers and their litters up to 30 mg/kg/day. In rabbits, the high dose level (200 mg/kg/day) did not induce any effects to fetuses.

Labor and Delivery
It is not known whether the use of dronedarone during labor or delivery has any immediate or delayed adverse effects. In pre- and post-natal development studies in the rat, at doses up to 50 mg/kg/day, dronedarone induced no effect on the duration of gestation or on parturition (see 16 NON-CLINICAL TOXICOLOGY, Reproduction16).

Pregnancy Testing
Verify that females of reproductive potential are not pregnant prior to initiating MULTAQ.

7.1.2 Breastfeeding

Dronedarone and its metabolites are excreted in rat milk. Nursing in lactating rats administered dronedarone was associated with minor reduced body-weight gain in the offspring.

It is not known whether this drug is excreted in human milk. Therefore, when dronedarone therapy is indicated, the mother should be advised to discontinue nursing) during treatment with MULTAQ and for 7 days (about 5 half-lives) after the final dose (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Safety and efficacy in children below the age of 18 years has not been established. Therefore, use in these patients is not recommended.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): a large number of elderly patients with AF or atrial flutter (AFL) have been included in the MULTAQ clinical program (more than 4500 patients aged 65 years or above, of which more than 2000 patients were 75 years or above). Efficacy and safety were comparable in both elderly and younger patients. Caution is needed in elderly patients≥ 75 years with multiple co morbidities.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile of dronedarone 400mg 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 12 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 pooled 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).

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

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Table 1 displays adverse reactions ≥ 1% associated with dronedarone 400 mg twice daily in AF or AFL patients, presented by system organ class and by decreasing order of frequency. Adverse reactions included in the system organ class “Investigation” are presented separately in **Table 2**.

Table 1 - Adverse reactions occurring ≥ than 1% of patients taking dronedarone in placebo-controlled clinical trials		
	Placebo (N=2875)	**Dronedarone 400 mg twice daily (N=3282)**
Gastrointestinal disorders		
Diarrhoea	5.8%	9.0%
Nausea	3.1%	4.9%
Abdominal pains	2.8%	3.5%
Vomiting	1.1%	2.0%
Dyspepsia	1.0%	1.5%
General disorders and administration site conditions		
Fatigue	3.6%	4.3%
Asthenia	1.7%	2.3%
Cardiac disorders		
Bradycardia	1.3%	3.3%
Skin and subcutaneous tissue disorders		
Rashes (including generalised, macular, maculo-papular)	1.6%	2.7%
Pruritus	0.9%	1.3%

8.3 Less Common Clinical Trial Adverse Reactions (<1%)

Nervous system disorders: Ageusia and dysgeusia.

Skin and subcutaneous tissue disorders: Dermatitis, dermatitis allergic, eczema, erythemas (including erythema and rash erythematous and photosensitivity reaction.

8.4 Abnormal laboratory findings: hematologic, clinical chemistry and other quantitative data

Clinical Trial Findings

In addition, the following laboratory data/ECG parameters were reported with dronedarone 400 mg twice daily.

Table 2 - : Laboratory data/ECG parameters		
	Placebo (N=2875)	**Dronedarone 400 mg twice daily (N=3282)**
Blood creatinine increased ≥ 10% five days after treatment initiation	20.6%	50.9%

Table 2 - : Laboratory data/ECG parameters		
	Placebo **(N=2875)**	**Dronedarone** **400 mg twice daily** **(N=3282)**
QTc Bazett prolonged (> 450 msec in male > 470 msec in female)	18.7%	27.6%

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval 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 disorders:
Congestive heart failure
A few cases of atrial flutter with 1:1 atrioventricular conduction have been reported.

Hepatic:
Serum hepatic enzymes and serum bilirubin increase: Hepatocellular liver injury, including acute liver failure requiring transplant, has been reported in a few patients (see 7 WARNINGS AND PRECAUTIONS).

Immune system disorders:
Anaphylactic reactions including angioedema

Renal:
Marked increase in serum creatinine, pre-renal azotemia and acute renal failure, often in the setting of heart failure (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular) 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. However, rare cases of acute renal failure resulting in death have been reported postmarketing. Although all such cases were complex and confounded by multiple illnesses and concomitant medications, a contributive role of dronedarone in the development of renal failure could not be excluded. Renal function should be monitored periodically (see 7 WARNINGS AND PRECAUTIONS, Renal).

Respiratory disorders:
Interstitial lung disease including pneumonitis and pulmonary fibrosis (a number of patients had been previously exposed to amiodarone).

Vascular disorders:
Vasculitis, including leukocytoclastic vasculitis (Schönlein-Henoch purpura)

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- strong CYP3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporin, clarithromycin, and ritonavir (see 2 CONTRAINDICATIONS)
- drugs inducing torsades de pointes such as phenothiazines, tricyclic antidepressants, certain oral macrolides, class I and III antiarrhythmics (see 2 CONTRAINDICATIONS)

9.2 Drug Interactions Overview

Dronedarone is primarily metabolized by CYP 3A4 (see 10.3 Pharmacokinetics) and is a moderate inhibitor of CYP 3A4 and a mild inhibitor of CYP 2D6. Therefore, inhibitors and inducers of CYP 3A4 have the potential to interact with dronedarone, and dronedarone has the potential to interact with medicinal products that are substrates of CYP 3A4 and CYP 2D6. It also has the potential to inhibit P-glycoprotein (P-gP) transport. Dronedarone and/or its metabolites also have the potential to inhibit Organic Anion Transporter (OAT), Organic Anion Transporting Polypeptide (OATP) and Organic Cation Transporter (OCT) transport *in vitro*. Dronedarone has no significant potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2C8 and CYP 2B6.

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

Co-administration of drugs prolonging the QT interval (such as phenothiazines, bepridil, tricyclic antidepressants, certain oral macrolides, Class I and III antiarrhythmics, which may induce torsades de pointes) is contraindicated because of the potential risk of proarrhythmia (see 2 CONTRAINDICATIONS).

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.

9.4 Drug-Drug Interactions

Table 3 - Established or Potential Drug-Drug Interactions

Agent	Ref	Effect	Clinical comment
Antidepressants	T	No effect Proarrhythmic effect	Dronedarone is a weak inhibitor of CYP2D6 in humans, so it is predicted to have limited interaction on antidepressants that are metabolized by CYP2D6. Co-administration of dronedarone with tricyclic antidepressants and other medicinal products inducing torsades de pointes is contraindicated (see **CONTRAINDICATIONS**).

Table 3 - Established or Potential Drug-Drug Interactions			
Agent	**Ref**	**Effect**	**Clinical comment**
Beta-blockers (e.g. metoprolol and propranolol	CT	↑ metoprolol and propranolol exposure	Beta-blockers that are metabolized by CYP 2D6 can have their exposure increased by dronedarone. Moreover, beta-blockers have the potential to interact with dronedarone from a pharmacodynamic point of view. Dronedarone 800 mg daily increased metoprolol exposure by 1.6- fold and propranolol exposure by 1.3- fold (i.e. much below the 6- fold differences observed between poor and extensive CYP 2D6 metabolizers).
		Bradycardia	In clinical trials, bradycardia was more frequently observed when dronedarone was given in combination with beta-blockers. Due to the pharmacokinetic interaction and possible pharmacodynamic interaction, beta-blockers should be used with caution if taken concomitantly with dronedarone.
Calcium antagonists (e.g. verapamil, diltiazem, nifedipine)	CT	↑ dronedarone exposure	Calcium antagonists are substrates and/or moderate inhibitors of CYP3A4. Moreover, calcium antagonists with heart-rate lowering properties have the potential to interact with dronedarone from a pharmacodynamic point of view. 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.
		↑ verapamil and nisoldipine exposure	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.
Clopidogrel	CT	No effect	No interaction was observed between dronedarone and clopidogrel.

Table 3 - Established or Potential Drug-Drug Interactions			
Agent	**Ref**	**Effect**	**Clinical comment**
Dabigatran	CT	↑ dabigatran exposure	Dronedarone **should not** be used concomitantly with dabigatran since it may increase exposure through P-gp inhibition, and thereby the risk of bleeding. When dabigatran etexilate 150 mg once daily was co-administered with dronedarone 400 mg twice daily, the dabigatran exposures (C_{max} and AUC_{0-24}) were increased by 1.7- and 2-fold, respectively. In a retrospective, claims database cohort study in the United States (US), no statistically significant increased risk of bleeding diagnoses leading to hospitalization or emergency department visit was observed with the concomitant use of dabigatran and dronedarone compared to those taking dabigatran alone in patients with non-valvular atrial fibrillation (NVAF). Among those concomitantly taking dabigatran and dronedarone, there was a statistically significant increased risk of ICD-diagnoses of gastrointestinal bleeding.
Digoxin	CT	↑ digoxin exposure	**Dronedarone (400 mg twice daily) increased digoxin exposure by 2.5-fold by inhibiting P-gP transporter. Moreover, digitalis has the potential to interact pharmacodynamically with dronedarone.** **In clinical trials, increased levels of digitalis were observed when dronedarone was co-administered with digitalis.** ***The concomitant use of digitalis and dronedarone is generally not recommended. Patients should be treated with digitalis and dronedarone only if there is a specific therapeutic need and no alternative treatment available.*** **These patients should be closely monitored for serum digoxin levels, especially during the first week of co-administration. Clinical and ECG monitoring are also recommended, and the digoxin dose should be adjusted as appropriate.**

Table 3 - Established or Potential Drug-Drug Interactions			
Agent	**Ref**	**Effect**	**Clinical comment**
Drugs prolonging the QT interval (e.g. phenothiazines, bepridil, tricyclic antidepressants, certain oral macrolides, Class I and III antiarrhythmics)	T	Proarrhythmic effect	Co-administration of drugs prolonging the QT interval (inducing torsades de pointes) is contraindicated because of the potential risk of proarrhythmia. (see **CONTRAINDICATIONS**).
Erythromycin (moderate CYP 3A4 inhibitor)	CT	↑ dronedarone exposure	Repeated doses of erythromycin (500 mg three times a day for 10 days) resulted in an increase in steady-state dronedarone exposure of 3.8-fold.
Factor Xa inhibitors (e.g. rivaroxaban, edoxaban, apixaban)	CT	↑ factor Xa inhibitor exposure	As dronedarone may increase exposure of factor Xa inhibitors through P-gp and/or CYP3A4 inhibition, an assessment of the risk for thromboembolic events and bleeding should be made when concomitant use is recommended. Consider dose reduction of the respective factor Xa inhibitors according to label recommendation. Dronedarone **should not** be used with rivaroxaban since it may increase exposure and thereby the risk of bleeding. In a retrospective cohort study using the Truven Health MarketScan database in the US, a significantly increased risk of ICD-diagnoses of bleeding leading to hospitalization or emergency department visit was observed, driven by gastrointestinal bleeding, in NVAF patients with the concomitant use of rivaroxaban and dronedarone compared to those taking rivaroxaban alone. Administration of dronedarone 400 mg twice daily for 7 days with a single concomitant dose of edoxaban 60 mg on Day 5 increased edoxaban AUC and C_{max} by 85% and 46%, respectively. Dose reduction of edoxaban is required for concomitant use with dronedarone. In a retrospective cohort study using the Truven Health MarketScan database in the US, no increased risk of bleeding diagnoses leading to hospitalization or emergency department visit was observed in NVAF patients with the concomitant use of apixaban with dronedarone compared to those taking apixaban alone.

Table 3 - Established or Potential Drug-Drug Interactions			
Agent	**Ref**	**Effect**	**Clinical comment**
Losartan (CYP 2C9 substrate)	CT	No effect	Although not considered to be a clinically significant interaction, co-administration of losartan 100 mg once daily for 14 days with dronedarone 400 mg bid decreased the C_{max} of losartan by 18% and the C_{max} and AUC_{0-24} of the active metabolite by 25% and 21% respectively.
Metformin (OCT1 and OCT2 substrate)	CT	No effect	No interaction was observed between dronedarone and metformin.
Omeprazole (CYP 2C19 substrate)	CT	No effect	No interaction was observed between dronedarone and omeprazole.
Oral contraceptives (e.g. ethinylestradiol and levonorgestrel	CT	No effect	No decreases in ethinylestradiol and levonorgestrel were observed in healthy subjects receiving dronedarone (800 mg twice daily) concomitantly with oral contraceptives. However, an increase of 28% in ethinylestradiol exposure and a 19% increase in levonorgestrel exposure were observed.
Pantoprazole	CT	No effect	Pantoprazole (40 mg once daily), a drug increasing gastric pH without any effect on cytochrome P450, had no significant pharmacokinetic interaction with dronedarone.
P-glycoprotein (P-gp) substrates (e.g. doxorubicin, fexofenadine and talinolol)	T	↑ P-gp plasma concentration	Dronedarone inhibits P-gP, and interactions may therefore occur with doxorubicin, fexofenadine and talinolol.
Potent CYP 3A4 inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin)	CT	↓ dronedarone exposure	Rifampicin (600mg once daily) decreased dronedarone exposure by 5-fold with no major change in its active metabolite exposure. Co-administration of rifampicin or other potent CYP3A4 inducers are not recommended with dronedarone as they decrease its exposure.

Table 3 - Established or Potential Drug-Drug Interactions			
Agent	**Ref**	**Effect**	**Clinical comment**
Potent CYP 3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, ritonavir, cyclosporin, clarithromycin)	CT	↑ dronedarone exposure	Repeated doses of ketoconazole (200 mg daily), a strong CYP 3A4 inhibitor, resulted in a 17-fold increase in dronedarone exposure. Concomitant use of ketoconazole as well as other potent CYP 3A4 inhibitors is contraindicated (see **CONTRAINDICATIONS**).
Sirolimus and Tacrolimus (CYP 3A4 substrates)	T	↑ sirolimus and tacrolimus exposure	Dronedarone can increase plasma concentrations of tacrolimus and sirolimus (CYP3A4 substrates) when given orally. Monitoring of their plasma concentrations and appropriate dosage adjustment is recommended when these drugs are co-administered with dronedarone
Statins (Substrates of CYP3A4 and/or P-gP substrates e.g. simvastatin, lovastatin, atorvastatin and pravastatin)	CT	↑ Simvastatin and simvastatin acid exposure	Dronedarone can increase exposure of statins that are substrates of CYP3A4 and/or P-gP substrates. Dronedarone (400 mg twice daily) increased simvastatin and simvastatin acid exposure by 4-fold and 2-fold respectively.
	CT	↑ atorvastatin, rosuvastatin	There was a weak interaction of dronedarone on atorvastatin (1.7-fold) and on statins transported by OATP, such as rosuvastatin (1.4-fold).
	T	↑ lovastatin, and pravastatin	It is predicted that dronedarone could also increase the exposures of lovastatin, and pravastatin within the same range as simvastatin acid. In clinical trials, there was no evidence of safety concerns when dronedarone was co-administered with statins metabolized by CYP3A4. As high doses of statins increase the risk of myopathy, concomitant use of statins which are CYP3A4 substrates and/or P-gP substrates should be undertaken with caution. Lower starting dose and maintenance doses of statins should be considered according to the statin label recommendations and patients monitored for clinical signs of muscular toxicity. A significant interaction of dronedarone on statins which are not CYP3A4/P-gP substrates such as fluvastatin is unlikely.

Table 3 - Established or Potential Drug-Drug Interactions			
Agent	**Ref**	**Effect**	**Clinical comment**
Theophylline (CYP 1A2 substrate)	CT	↓ theophylline exposure	Concomitant administration of dronedarone 400 mg bid with theophylline 400 mg bid resulted in decreased theophylline exposure (18% decrease in AUC_{0-12} and a 17% decrease in C_{max} of theophylline).
Warfarin and other vitamin K antagonists (CYP 2C9 substrate)	CT	↑ S-warfarin exposure	Dronedarone (600 mg twice daily) increased S-warfarin by 1.2- fold with no change in R-warfarin and increased INR by only 1.07-fold. In the ATHENA study, more patients taking oral anticoagulants experienced clinically significant INR elevations (≥5) within 1 week of starting dronedarone (4.7%) versus placebo (1.7%). The dose of oral anticoagulant at baseline and any change in dose were not monitored, but after 1 month, there were no further differences between the treatment groups. Furthermore, no excess risk of bleeding was observed in the dronedarone group. Increased INR (≥5) values with or without bleeding events were reported in post-marketing cases in patients treated concomitantly with oral vitamin K antagonists and dronedarone. In 70% of these cases, this increase occurred within 2 weeks of starting dronedarone. In 80% of the cases where the dose of the anticoagulant was adjusted, INR recovered to therapeutic values. INR should be monitored closely for the first 6 weeks after initiating dronedarone treatment in patients taking vitamin K antagonists.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Grapefruit juice
Repeated doses of 300 mL of grapefruit juice (inhibitor of the CYP3A4) three times daily resulted in a 3-fold increase in dronedarone exposure. Therefore, patients should be warned to avoid grapefruit juice beverages while taking dronedarone.

9.6 Drug-Herb Interactions

Co-administration of St John's Wort, a potent CYP3A4 inducer, is not recommended with dronedarone as this herb decreases its exposure.

10 CLINICAL PHARMACOLOGY

Human Pharmacodynamics

Increase in Serum Creatinine

ANDROMEDA, a study performed in 627 patients with left ventricular dysfunction and a recent hospitalization for a severe episode of congestive heart failure was stopped prematurely due to an excess of deaths in the dronedarone group[n=25 versus 12 (placebo), p=0.027].

Exploration of the ANDROMEDA findings suggests that increased values of plasma creatinine could be misinterpreted and lead to inappropriate discontinuation of ACE inhibitors or AIIRAs in patients requiring this treatment.

While the proportion of patients treated with ACE inhibitors/AIIRAs at baseline was similar in the placebo and dronedarone groups, 84.2% and 88.4%, respectively, the proportion of patients discontinuing these agents during the study was higher in the dronedarone group 13.2% compared to placebo (5.7%).

Therefore, in the ATHENA trial (see 14 CLINICAL TRIALS) which excluded patients in an unstable hemodynamic condition including congestive heart failure of stage NYHA IV (see 2 CONTRAINDICATIONS) the possibility of a creatinine increase with dronedarone and its appropriate interpretation were explained to investigators, with the recommendation not to inappropriately discontinue ACE inhibitors or AIIRAs in patients requiring this treatment (see 7 WARNINGS AND PRECAUTIONS, Renal and 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

10.1 Mechanism of Action

In animals, dronedarone prevents atrial fibrillation or restores normal sinus rhythm depending on the model used. It also prevents ventricular tachycardia and ventricular fibrillation in several animal models. These effects most likely result from its electrophysiological properties belonging to all four Vaughan-Williams classes. Dronedarone is a multichannel blocker inhibiting the potassium currents (including $I_{K(Ach)}$, I_{Kur}, I_{Kr}, I_{Ks}) and thus prolonging cardiac action potential and refractory periods (Class III). It also inhibits the sodium currents (Class Ib) and the calcium currents (Class IV). It non-competitively antagonizes adrenergic activities (Class II).

10.2 Pharmacodynamics

In animal models, dronedarone reduces heart rate. It prolongs Wenckebach cycle length and AH-, PQ-, QT- intervals; with no marked effect on QTc-, HV- and QRS- intervals. It increases effective refractory periods of the atrium, atrio-ventricular node and ventricle with 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, more pronounced in coronary arteries (related to the activation of the nitric oxide pathway) than in peripheral arteries.

Dronedarone displays indirect antiadrenergic effects; it reduces alpha-adrenergic blood pressure response to epinephrine and beta1 and beta2 responses to isoproterenol.

Animal Pharmacodynamics

***In vitro* pharmacology**

The *in vitro* pharmacology activities of dronedarone were similar to those of amiodarone but with a higher potency of dronedarone in most studies. The in vitro electrophysiological studies demonstrated that dronedarone (0.01 to 30 µmol/L), as well as amiodarone, is a multi-channel blocker since it inhibits, through a direct interaction, several native ionic channels of cardiomyocytes: rapid sodium channel and L-type and T-type calcium currents, outward potassium currents: I_{K1}, I_{Kr}, I_{Ks}, I_{sus} and $I_{K(ACh)}$ and the pacemaker current If, and recombinant human channels human Ether-a-go-go Related Gene (hERG), (I_{Kr}) and Kv1.5 (I_{Kur}) stably transfected in CHO/human embryonic kidney (HEK) cells.

Among the inward currents, dronedarone had binding affinity for and inhibited the rapid sodium channel. Thus, it reduced the rate of phase 0 of the Action Potential (AP) (dV/dt_{max}) in atrium and ventricle, since dV/dt_{max} is a reasonable indicator of changes in the sodium current. The decrease in dV/dt_{max} by the drug was frequency-dependent, particularly at high rates (100 and 200 beats/min) and with rapid onset kinetics; an effect characteristic of class IB antiarrhythmic agents like lidocaine and also amiodarone.

Dronedarone also had binding affinity for and blocked L-type calcium channels use dependently with rapid onset kinetics and thus displayed calcium antagonistic activity and class IV antiarrhythmic properties. This finding was in accordance with a reduction in the calcium transient (intracellular calcium concentration) and a decrease in shortening (contraction parameter) of isolated ventricular cells or with a reduction of contraction amplitude of isolated atrium, ventricle and heart.

The main potassium currents involved in cardiac repolarization are I_{to}, I_{K1}, I_{Kr}, I_{Ks} and I_{sus} at the ventricular level, plus $I_{K(ACh)}$ and I_{Kur} in the atrium. Dronedarone weakly increased I_{to}, weakly decreased I_{K1} but concentration-dependently reduced I_{Kr}, I_{Ks}, $I_{K(ACh)}$ and $I_{Kv1.5}$. At the atrial level, the APD lengthening observed in rabbit atria might be explained by the inhibition of one of these currents involved in repolarization phase. Dronedarone also blocked the carbachol induced $I_{K(ACh)}$ in atrial cells. These results suggested that dronedarone could effectively antagonize the AP shortening induced by vagal stimulation, as has been demonstrated with amiodarone which inhibits the carbachol-induced APD shortening; dronedarone is thus likely to have antiarrhythmic activity in pathologies where an increase in vagal tone might play a role such as, for example, atrial fibrillation.

Dronedarone showed vasodilatory properties: it caused concentration-dependent decreases in K+ depolarization- and norepinephrine-induced contraction of aortic strips and decreased coronary resistance of isolated hearts perfused at constant pressure. All these effects of dronedarone might be related, at least in part, to its calcium antagonistic or class IV antiarrhythmic property. However in coronary arteries, as its vasodilating effect was inhibited by a nitric oxide synthase inhibitor, L-NOARG, the coronary-dilator effect of dronedarone was probably related to activation of the nitric oxide pathway.

***In vivo* pharmacology**

The *in vivo* electrophysiological and hemodynamic profiles as well as anti-adrenergic activities of dronedarone were similar to those of amiodarone.

Dronedarone decreased heart rate (HR) in the majority of experiments carried out in anesthetized or conscious rats, dogs and pigs. Dronedarone increased both Atrial effective refractory period (ERP) and

Atrio-ventricular (AV) nodal ERP whereas ventricular ERP was slightly prolonged with a minimal degree of reverse frequency-dependency. With the reduction in HR, ventricular interval duration (QT) on the electrocardiogram (ECG) was often prolonged but corrected QT (QTc) was rarely prolonged. These acute electrophysiological effects of dronedarone tended to be enhanced after chronic oral dosing.

The multifactorial mechanism of action of dronedarone contributed to its hemodynamic effects. Dronedarone had α_1-, β_1- and β_2-anti adrenergic effects (although there was weak affinity for these receptors) and calcium antagonist properties that might contribute to the vasodilating and, possibly, to the negative inotropic effects. Also, dronedarone transiently increased coronary blood flow in dogs. Main hemodynamic effects of dronedarone were a decrease in contractility (LV dP/dt_{max}) and an increase in LV end diastolic pressure observed at relatively high concentrations and after intravenous administration.

Chronic oral treatment with dronedarone also decreased plasma concentrations of noradrenaline and these changes correlated with the reduction of HR. This observation suggested that the reduction in the release of catecholamines might participate in the antiadrenergic action of dronedarone as well as the non-competitive β-adrenoceptor antagonistic activity, the down-regulation of the β-adrenoceptor and calcium antagonistic property. A direct activation of α2 presynaptic adrenoceptors seems unlikely since dronedarone has a weak affinity for α2 receptors (IC50 = 28 µmol/L) and the peak plasma concentration (1.3 to 1.9 µmol/L) was much lower.

10.3 Pharmacokinetics

Table 4 - Summary of MULTAQ's Pharmacokinetic Parameters in healthy young male subjects

Single dose mean	C_{max}	$t_{½}$ (h)	$AUC_{0-\infty}$	Clearance	Volume of distribution
400 mg	67.2 (36)	17.6 (56)	474 (33)	937 (35)	21000 (31)

Absorption:
Dronedarone should be taken with food. Following oral administration in fed conditions, dronedarone is well absorbed (at least 70 %) from intestines to blood. 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. 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 mean dronedarone C_{max} 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_{max} 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 (Vss) ranges from 1200 to 1400 L

Metabolism:
Dronedarone is extensively metabolized, mainly by CYP3A4. 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. Monoamine oxidases contribute partially to the metabolism of the active metabolite of dronedarone. The N-debutyl metabolite exhibits pharmacodynamic activity but is 3 to 10-times less potent than dronedarone.

Excretion:
After oral administration, approximately 6 % of the labeled dose is excreted in urine mainly as metabolites (no unchanged compound excreted in urine) and 84 % are excreted in feces 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 and Conditions

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 CYP3A4 inhibitors) remain modest in their magnitude (less than 2- fold).

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.

Gender
In female patients, dronedarone exposures are on average 30% higher as compared to male patients (see 8.1 Adverse Reactions Overview).

Race
Pharmacokinetic differences due to race were not assessed.

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 (see 7.1 WARNINGS AND PRECAUTIONS, Special Populations).

Pediatric population
The pharmacokinetics of dronedarone were not assessed in pediatric patients.

Liver Impairment
In subjects with moderate hepatic impairment, dronedarone total and unbound exposures are

increased by 1.3-fold and by 2-fold respectively. Those of the active metabolite are decreased by 1.6-fold to 1.9-fold. The effect of severe hepatic impairment on the pharmacokinetics of dronedarone was not assessed (see 2 CONTRAINDICATIONS).

Renal Impairment
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 7.1 WARNINGS AND PRECAUTIONS, Special Populations).

Detailed Pharmacokinetics
Absorption and Bioavailability
Dronedarone appeared to be well absorbed (64 to 95% of the administered dose) following single oral administration in both rats and dogs, based on combined urinary and biliary excretion of radioactivity, and on percentage of parent drug excreted in feces that is likely non-absorbed. Dronedarone underwent an enterohepatic circulation involving about 11% of the dose over 24 hours post dosing as measured in rats intraduodenally infused with the bile of rats pretreated with dronedarone. As a result of the first pass extraction, the absolute oral bioavailability of dronedarone was low (14 to 22%) in rats and dogs and was similar to that found in humans (15%). SR35021 exposure represented around 22 to 28% of that of dronedarone in rats and around 11% in dogs. In mice, SR35021 achieved plasma levels roughly similar to those of dronedarone.

In toxicokinetic studies, AUC and C_{max} generally increased more than expected by dose proportionality in rats, rabbits and dogs while they increased roughly in proportion to dose in mice. No significant accumulation of parent drug and SR35021 was observed following repeated oral administration in mice and dogs, while a 2- to 3-fold increase in dronedarone and SR35021 exposure was observed in rats. Steady state was generally already achieved on day 14 of the multiple dose and toxicology studies in mice, rats and dogs whatever the dose, except in rats for doses above and including 17.5 mg/kg/day (later achievement between 1 and 3 months of treatment). No major gender effect was observed.

Distribution and Protein Binding
Following both single and multiple oral administrations to rats and dogs, circulating radioactivity was mainly distributed in plasma rather than in blood cells, independent of the route or duration of administration.

Dronedarone and SR35021 were very highly bound to plasma proteins (>99.5% for dronedarone and >98% for SR35021) in all animal species tested (mice, rats, rabbits, dogs, macaques) and humans, ranging from 99.7 to 99.9%. No saturation of protein binding was observed within the range of concentrations tested (1 to 10 000 ng/mL for dronedarone and 50 to 10 000 ng/mL for SR35021) encompassing largely those reached in all animal species and in human.

In rats, dogs and macaques, the pharmacokinetics of dronedarone was characterized by a large volume of distribution. Tissue distribution was investigated in male and female albino rats and in pigmented male rats following single dose and in male albino rats following repeated doses. Both qualitative and quantitative distribution studies were performed. Radioactivity was rapidly and extensively distributed in various tissues. In addition to the gastro-intestinal tract, high concentrations of total radioactivity were observed in the liver and kidney at each timepoint. Radioactivity was also distributed in pituitary

gland, lung, adrenals, pancreas, spleen, thyroid, salivary glands, brown fat, Harder's glands, pineal body and heart. Actual concentrations of total radioactivity were higher following multiple doses, but radioactivity was rapidly eliminated such that the concentrations decreased markedly by 24 hours post dose and were below the limit of quantification between 96 and 336 hours after the last dose. A similar pattern of distribution and elimination of total radioactivity was observed following both single and multiple oral doses of
10 mg/kg [^{14}C]-dronedarone to male rats. At higher doses of 25 and 100 mg/kg affinity of radioactivity for mesenteric lymph nodes was assessed to support carcinogenicity studies. Radioactivity concentration in mesenteric lymph nodes was 2- to 8-fold higher than in mandibular lymph nodes and 5- to 38-fold higher than in blood after single or 28-day repeated administrations. Radioactivity showed an affinity for melanin containing tissues (uveal tract, eye and skin) in male-pigmented rats.

Radioactivity was shown to cross the placental barrier in the rat and in the rabbit, and was detected in fetuses in addition to the fetal area (trophoblast and placenta).

Metabolism
Overall, at least 30 metabolites have been detected in the different studied species. The main routes of biotransformation consisted in:

- *N*-debutylation leading to SR35021 with further oxidation;
- Oxidative deamination leading to the O-propanoic acid derivative (SR90154) with further oxidation;
- Oxidation of the parent compound.

SR35021 has antiarrhythmic, electrophysiological and hemodynamic activities similar to those of dronedarone but is 3 to 10 times less potent than dronedarone. Hence, SR35021 may contribute to the pharmacological activity of dronedarone but not to a major extent. SR90154 has very little or no activity.

Dronedarone undergoes extensive metabolism after oral administration with less than 15% excreted unchanged. In plasma, following single oral administration, dronedarone accounted for approximately 4 to 45% of total radioactivity across species. Numerous metabolites were identified. The main circulating metabolites were SR35021 (N-debutylated metabolite) in mice, SR90154 (propanoic acid derivative) in rats and dogs and oxidated derivatives of dronedarone, SR35021 and SR90154 in rabbits. In human, the main circulating metabolites were SR90154 and SR35021, with plasmatic exposures similar or higher to dronedarone. Exposures estimated in animals for those two metabolites during long term toxicology studies (muse, rat dog) at NOEL or at 1st dose with effects, showed levels in the range or higher than exposure expected in human at the therapeutic dose.

Various oxidative derivates from dronedarone, SR35021 and SR90154 were also circulating in human, accounting for 1.1 to 5.8 % of total radioactivity. These metabolites were generally quantified in plasma from animal species for 1.8 to 21% of total radioactivity. Three circulating human metabolites from secondary oxidation pathways (Trihydroxy derivative of dronedarone and N-ethanol derivatives of SR35021) could not be quantified in animal plasma but were observed, or their direct precursor, in excreta of at least one animal species.

The different animal species were representative of the main metabolite pathways observed in human. This support that animals in toxicological studies were exposed to the main human metabolites.

Excretion and Elimination
In rats, dogs and macaques, the pharmacokinetics of dronedarone were characterized by a high plasma clearance and a moderate terminal half-life. Dronedarone is rapidly eliminated by metabolic clearance with no excretion of unchanged drug in urine (mouse, rat, rabbit, dog, macaque), and less than 0.5% of unchanged drug in rat bile. In most of the studied species, following oral administration, 72% to 97% of total radioactivity was excreted in feces. Around 44% and 69% of the dose was recovered in the 0-48 hour rat bile collection period following oral and intravenous administrations, respectively. Urinary excretion of radioactivity was less than 9% of the dose, whatever the species. In feces, dronedarone represented 5% to 12% of the administered dose whatever the species examined and could represent non-absorbed drug. These data demonstrate that metabolism followed by biliary excretion is the main pathway for dronedarone elimination.

The daily excretion of radioactivity in feces remained constant from day 1 to day 14 during the repeated dosing regimen in mice and dogs and slightly increased in rats (80% of a dose on day 1 to 106% on day 14 over the 0-24 hour period). Over a 168-hour period, total recovery after single dosing was more than 90% in all species examined, indicating that drug excretion was almost complete.

Radioactivity was excreted in milk after treatment of lactating dams.

11 STORAGE, STABILITY AND DISPOSAL

Store at 25°C, with excursion permitted between 15 and 30°C.

Store in the original package.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Non-proprietary name of the drug product(s): Dronedarone hydrochloride

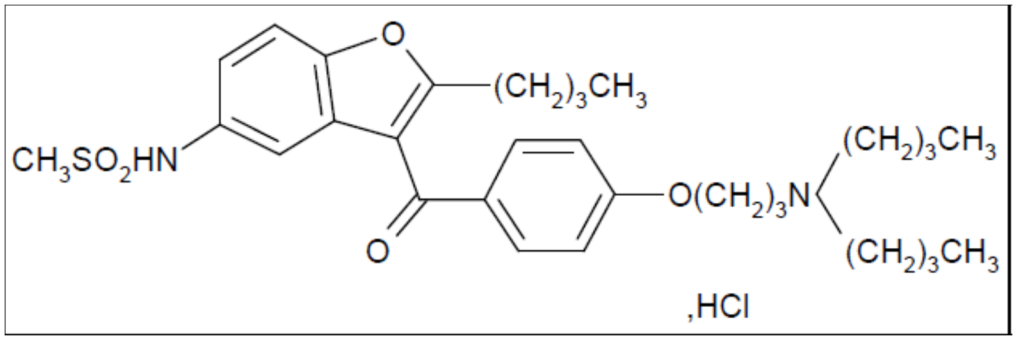
Chemical name:

N-{2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl} methanesulfonamide, hydrochloride.

Molecular formula and molecular mass:

Its empirical formula is $C_{31}H_{44}N_2O_5S$, HCl with a relative molecular mass of 593.2 (556.8 for dronedarone base).

Structural formula:



Physicochemical properties: Dronedarone HCl is a white to practically white fine powder that is practically insoluble in water and freely soluble in methylene chloride and methanol.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

14.1.1 Atrial Fibrillation

The efficacy of dronedarone in the reduction of risk of cardiovascular hospitalization or death from any cause was demonstrated in patients with atrial fibrillation (AF) or a history of AF/AFL and additional risk factors in the ATHENA multicenter, multinational, double blind, and randomized placebo-controlled study. Patients were to have at least one risk factor (including age, hypertension, diabetes, prior cerebrovascular accident, left atrium diameter ≥ 50 mm or LVEF<0.40) together with AF/AFL and sinus rhythm both documented within the last 6 months. Patients could be in AF/AFL or in sinus rhythm after spontaneous conversion or following any procedures. Four thousand six hundred and twenty eight (4628) patients were randomized and treated for up to 30 months maximum (median follow-up: 22 months) with either dronedarone 400 mg twice daily (2301 patients) or placebo (2327 patients), in

addition to conventional therapy including beta-blockers (71%), ACE inhibitors or angiotensin receptor blockers (ARBs) (69%) digitalis (14%), calcium antagonists (14%), statins (39%), oral anticoagulants (60%), chronic antiplatelet therapy (5 %) and/or diuretics (54%).

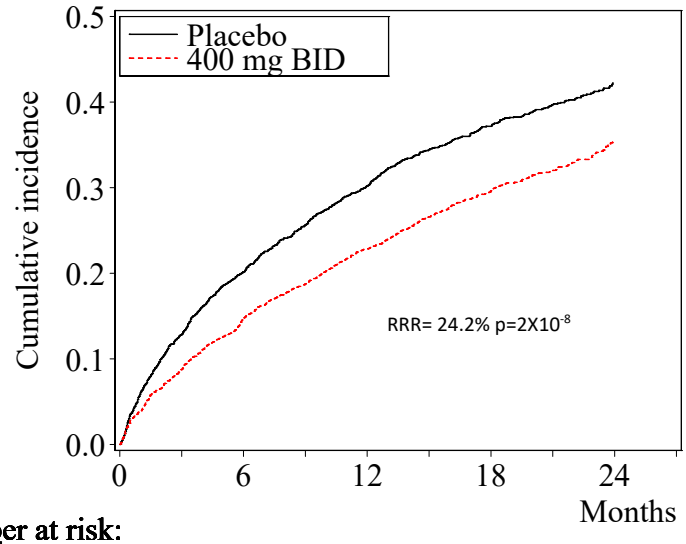
The primary endpoint of the study was the time to first hospitalization for 'cardiovascular reasons' or death from any cause. With few exceptions, the 17 components comprising 'cardiovascular hospitalization' included many not generally accepted as being causally related to atrial fibrillation. Secondary endpoints evaluated were time to death from any cause, time to first hospitalization for 'cardiovascular reasons'. Time to cardiovascular death and time to sudden death were 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 had hypertension (86%) and structural heart disease (60% - which included coronary artery disease, congestive heart failure and left ventricular ejection fraction <45%. Twenty five percent (25%) had AF at baseline.

Dronedarone reduced the incidence of cardiovascular hospitalization or death from any cause by 24.2% when compared to placebo.

The curves showing the overall event rate are displayed in Figure 1.

Figure 1 – Kaplan-Meier cumulative incidence curves from randomization to first cardiovascular hospitalization or death from any cause truncated at 24 months



Number at risk:					
Placebo	2327	1858	1625	1072	385
400 mg BID	2301	1963	1776	1177	403

The results pertaining to the primary composite endpoints and its components are presented in Table 5.

Table 5- Efficacy Results: ATHENA Study					
Type of event	**Time points**	**Percentages of events (*)**		**Absolute reduction/ increase (%)**	**Relative reduction/ increase (%)**
		Placebo (N=2327)	**Dronedarone 400 mg bid (N=2301)**	**Dronedarone compared with placebo**	**Dronedarone compared with placebo**
Primary efficacy endpoint (**)	1 - year	30.2%	22.8%	-7.4%	-24.50%
	2 - year	42.2%	35.4%	-6.8%	-16.11%
Cardiovascular hospitalization (total)	1 - year	28.9%	21.7%	-7.2%	-24.91%
	2 - year	39.9%	32.6%	-7.3%	-18.30%
Cardiovascular hospitalization with main reason being AF and other supraventricular rhythm disorders(***)	1 - year	17.1%	10.1%	-7.0%	-40.94%
	2 - year	22.6%	15.7%	-6.9%	-30.53%
Cardiovascular hospitalization with main reason being all other causes	1 - year	14.1%	12.9%	-1.2%	-8.51%
	2 - year	22.3%	20.0%	-2.3%	-10.31%
Death from any cause	1 - year	1.8%	1.5%	-0.3%	- 16.67%
	2 - year	3.9%	4.2%	+0.3%	+7.69%

(*) Extracted from the Kaplan-Meier estimation
(**) primary endpoint composition: 'cardiovascular hospitalization' or death from any cause
Note: death, cardiovascular or non-cardiovascular, were only those not preceded by hospitalization
(***) See Table 6 below

As can be seen from Table 6, it was a reduction in the recurrence of atrial fibrillation and other supraventricular rhythm disorders that resulted in the reduction in hospitalization for 'cardiovascular reasons'. Hospitalizations for all other reasons were very similar in both dronedarone and placebo groups.

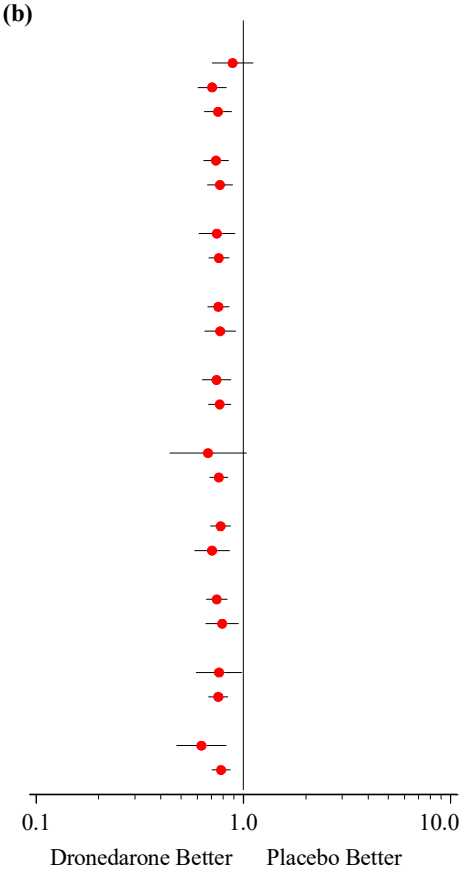
Table 6-Number (%) of patients with a cardiovascular hospitalization according to pre specified main reason per the Investigator during on-study period – all randomized patients (EFC5555/ATHENA)

	Placebo (N=2327)		Dronedarone 400 mg BID (N=2301)	
Any cardiovascular hospitalization	859	(36.9%)	675	(29.3%)
Atrial fibrillation and other supraventricular rhythm disorders	**457**	**(19.6%)**	**296**	**(12.9%)**
Worsening CHF, including pulmonary edema or dyspnea of cardiac origin	92	(4.0%)	78	(3.4%)
Myocardial infarction or unstable angina	61	(2.6%)	48	(2.1%)
Stable angina pectoris or atypical chest pain	41	(1.8%)	45	(2.0%)
TIA or stroke (except intracranial hemorrhage)	35	(1.5%)	28	(1.2%)
Transcutaneous coronary, cerebrovascular or peripheral procedure	31	(1.3%)	27	(1.2%)
Implantation of a pacemaker, ICD or any other cardiac device	29	(1.2%)	32	(1.4%)
Major bleeding (requiring two or more units of blood or any intracranial hemorrhage)	24	(1.0%)	21	(0.9%)
Syncope	24	(1.0%)	21	(0.9%)
Cardiovascular surgery except cardiac transplantation	23	(1.0%)	21	(0.9%)
Blood pressure related (hypotension, hypertension; except syncope)	21	(0.9%)	21	(0.9%)
Atherosclerosis related (if not otherwise specified)	8	(0.3%)	11	(0.5%)
Ventricular tachycardia (non-sustained and sustained VT)	6	(0.3%)	6	(0.3%)
Pulmonary embolism or deep vein thrombosis	3	(0.1%)	10	(0.4%)
Non-fatal cardiac arrest	2	(<0.1%)	3	(0.1%)
Ventricular extrasystoles	1	(<0.1%)	1	(<0.1%)
Ventricular fibrillation	1	(<0.1%)	1	(<0.1%)
Cardiovascular infection	0	(0%)	4	(0.2%)
Other ventricular arrhythmia	0	(0%)	1	(<0.1%)

The reduction in 'cardiovascular hospitalization' or death from any cause was consistent in all subgroups, irrespective of baseline characteristics or concomitant medications (see **Figure 2**).

Figure 2– Relative risk (dronedarone 400 mg BID versus placebo) estimates with 95% confidence intervals according to selected baseline characteristics-first cardiovascular hospitalization or death from any cause

Characteristic	N	RR [95% CI] (a)	P-value (b)
Age (years)			
<65	873	0.89 [0.71;1.11]	
[65-75[	1830	0.71 [0.60;0.83]	
>=75	1925	0.75 [0.65;0.87]	0.27
Gender			
Male	2459	0.74 [0.64;0.85]	
Female	2169	0.77 [0.67;0.89]	0.65
Presence of AF/AFL			
Yes	1155	0.74 [0.61;0.91]	
No	3473	0.76 [0.68;0.85]	0.85
Structural Heart Disease			
Yes	2732	0.76 [0.67;0.85]	
No	1853	0.77 [0.65;0.92]	0.85
LVEF<35% or NYHA>=class I			
Yes	1417	0.74 [0.63;0.87]	
No	3146	0.77 [0.68;0.87]	0.71
LVEF(%)			
<35	179	0.68 [0.44;1.03]	
>=35	4365	0.76 [0.69;0.84]	0.58
Beta blocking agents			
Yes	3269	0.78 [0.69;0.87]	
No	1359	0.71 [0.58;0.86]	0.41
ACE or AII receptor antagonists			
Yes	3216	0.74 [0.66;0.83]	
No	1412	0.79 [0.66;0.95]	0.59
Digitalis			
Yes	629	0.76 [0.59;0.98]	
No	3999	0.76 [0.68;0.84]	0.96
Calcium antagonists (c)			
Yes	638	0.63 [0.48;0.82]	
No	3990	0.78 [0.70;0.87]	0.15



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

With respect to the secondary endpoint of 'death from any cause', the difference between the number of deaths in the two treatment groups did not reach statistical significance (p=0.1758).

15 MICROBIOLOGY

No microbiological information is available for this drug product.

16 NON-CLINICAL TOXICOLOGY

Single-Dose Toxicity

Single dose toxicity studies with oral (1500 and 2000 mg/kg) or intravenous (up to 20 mg/kg) dronedarone administration were performed in mice and rats of both sexes.

Orally, the maximum nonlethal dose in the mouse and the rat was 2000 mg/kg. A single oral administration of 2000 mg/kg of dronedarone caused some clinical signs in rats only (prostration, piloerection, ptyalism, and soiled urogenital areas), and a decrease in body weight gain in both species. No target organ could be identified. After intravenous administration, the maximum nonlethal dose

was 10 mg/kg in mice and rats of both sexes. Physical signs included decubitus, prostration, decreased activity and sometimes red urine.

The findings from the oral studies suggest that dronedarone has a very limited potential for toxicity in humans in acute overdose situations.

Repeat-Dose Toxicity

In the pivotal subacute and chronic toxicity studies, dronedarone was administered from 2 to 160 mg/kg/day in rats from 2 weeks to 6 months and from 5 to 140 mg/kg/day in dogs from 2 weeks to 1 year by the oral route.

Health deterioration changes, subsequent to the other treatment-related effects described below, were observed at doses higher than 60 mg/kg/day. Health deterioration was clearly dose related throughout the studies conducted with dronedarone.

Signs of health deterioration were marked at the high dose of 160 mg/kg/day in rats and led to mortality in 4/20 rats from day 14 to day 16 in the 2 week study after a decline in health status: clinical signs of poor condition were characterized by piloerection, reduced activity, soiled urogenital area, occurring mainly in the second week of the study and was associated with weight loss and decreased food consumption.

The presence of a poor general health condition was supported at histopathological examination by the occurrence with classical health deterioration changes consisting of fat tissue atrophy, decreased hepatocytic margination (indicative of decreased physiological glycogen storage) and reduced size of hepatocytes, renal cortical tubular distensions, atrophy of crural muscle, atrophy (serous dedifferentiation) in the pancreas, parotid and submaxillary glands, atrophy of the small intestine mucosa, lymphoid atrophy of the thymus (involution) or lymph nodes, hyperplasia, necrosis or hemorrhage in the adrenal cortex, fatty involution of the bone marrow, thinning of primary spongiosa in the proximal tibial epiphysis, spermatogenesis changes and atrophy of the male sexual glands.

In the chronic studies in the rat (up to 6 months) and dog (up to 1 year), health deterioration was slight and noted only at the highest dose and mainly shown by weight loss or decreased weight gain associated with decreased food consumption, with a tendency for recovery during the chronic studies.

In subacute and chronic toxicity studies, slight and reversible phospholipidosis (accumulation of foamy macrophages) was observed in mesenteric lymph nodes mainly in the rat. This effect is considered specific to this species and not relevant to humans.

Electrocardiographic changes were noted at 160 mg/kg/day in the 2 week study and at all dose levels in the chronic studies in rats and, in dogs, from 25 mg/kg/day upwards in the 2 week study, at 60 mg/kg/day in the 3 month study and at 45 mg/kg/day in the 1 year study in dogs, which consisted of decreased HR and increased PR and QT (associated with increased QTc only during the 1 year study), sometimes associated with slightly increased heart weight. These variations were related to the pharmacological properties of the test compound. No ventricular premature complex, no ventricular tachycardia or ventricular fibrillations were observed in any of the studies and there was no death associated with cardiac effects.

No mortality other than that imputed to nonspecific effects in rats at 160 mg/kg/day was attributed to the compound. It should be noted that no sudden death occurred during any of the studies.

Dronedarone was well tolerated up to and including 60 mg/kg/day in the 3-month rat and 3-month dog studies, up to 50 mg/kg/day in the 6 month rat study and up to 45 mg/kg/day in the one year dog study.

Genotoxicity
Dronedarone had no genotoxic effects, based on one *in viv*o micronucleus test in mice and four *in vitro* tests: the Ames test with or without metabolic activation, a DNA repair test on rat hepatocytes, a gene mutation assay on hamster fibroblasts and a cytogenetic study of human lymphocytes.

Carcinogenicity
In 2 year-oral carcinogenicity studies, the highest dronedarone dose administered for 24 months was 70 mg/kg/day in rat and 300 mg/kg/day in mice. Observations were increased incidence of mammary gland tumors in female mice, histiocytic sarcomas in mice and hemangiomas at the mesenteric lymph node level in rats, all at the highest tested dose only (corresponding to an exposure of 5 to 10 times that of the human therapeutic dose).

Mammary gland adenocarcinomas/adenoacanthomas were observed in female mice, with statistical significance at 300 mg/kg/day for adenocarcinomas when compared to the control groups. As mammary tumors are known to be influenced by hormones, prolactin levels were measured in two separate studies and were shown to be slightly increased with a statistically significant difference in treated animals compared to controls. The presence of malignant epithelial tumors in the mammary gland of female mice was not considered to represent a significant risk factor for humans for the following reasons:

- These tumors were limited to one sex and one species and high dose group.
- These changes were not associated with any target organ toxicity.
- The morphology of these neoplasms is very species specific and similar neoplasms are not observed in human breast cancer.
- The limited increase in tumor incidence was proved to be associated with a consistently moderate increase in prolactin, and the human relevance of rodent prolactin induced mammary carcinogenesis is believed to be low.

- ***Histiocytic sarcomas (hemolymphoreticular system)*** observed in mice at the highest dose were not considered to represent a significant risk factor for humans due to the following reasons:

- These changes were observed at a low incidence, with no similar effects in male or female rats, and the relevance of such marginal findings remained equivocal since this could be the result of a normal variation or represent a weak carcinogenic response. There is a great variability of background incidence and this may also be partly attributed to the variety of terminology used.
- The incidences were similar in magnitude to published incidences in untreated male and female mice from a large reference study.

- No chemical products induce histiocytic sarcoma in rats; in mice, three compounds are known to cause such changes, two of them are clearly genotoxic and the remaining one has not undergone a complete battery of genotoxic tests.
- There was no increase in the frequency of other lymphoreticular tumors in both carcinogenicity studies.
- No analoguous neoplasm is known to occur in humans.

- ***Benign hemangiomas*** observed in the mesenteric lymph nodes in the rat, at the highest dose only were not considered to be relevant for human:

- It is known that hemangiomas are not precancerous changes and do not transform into malignant hemangiosarcomas in either animals or man.
- Hemangiomas in man are relatively common in many organs and in many cases are present over the lifespan of an individual but hemangiomas and hemangiosarcomas of lymph nodes are extremely rare in humans.
- Spontaneous proliferative vascular changes similar to those observed in the rat mesenteric lymph node have been described in mesenteric lymph node in man but are considered completely innocuous. In the literature, it is described how venous or lymphatic obstruction leads to vascular transformation of lymph nodes. The increased incidence in the rat is considered to be in relation with phospholipidosis and accumulation of foamy macrophages in the mesenteric nodes seen in this species, particularly susceptible to this type of effect. It was actually shown that dronedarone accumulates preferentially in the mesenteric lymph nodes when compared with other lymph nodes and with plasma. Thus, the proliferative vascular changes seen in the rat are considered to be reactive-proliferative, rare in occurrence and innocuous, therefore not relevant for man.
- In conclusion, only the high dose group was involved in both species for these neoplastic changes and an acceptable exposure multiple (5 to 10) exists between the plasma exposures at which an increased incidence of tumors is seen, and the exposure in man at the expected human therapeutic dose. Additionally, none of these observations was considered relevant for humans.

Reproductive and Developmental Toxicity
Dronedarone was not shown to alter fertility in animal studies up to 100 mg/kg/day because the treatment did not induce any adverse effect upon mating performance and fertility or male reproductive organ weights and sperm motility and count at any dosage.
Dronedarone is teratogenic in the rat at 100 mg/kg/day. The dose level of 50 mg/kg/day, at which a ratio exposure between rat and human at therapeutic dose is around 3, is not teratogenic.
Dronedarone is not teratogenic in rabbits at 60 mg/kg/day. Although the number of litters was low at the dose level of 200 mg/kg/day, it was considered as nonteratogenic. In the light of these findings, dronedarone should be contraindicated in pregnant women. The effects of this compound on the development of offspring (decreased viability indices during lactation at high dose levels, i.e. 90 mg/kg/day) were noted however, the most important changes were the marked tissue concentration and the potential effects on the thyroid function of the fetus.

It is not known whether dronedarone is excreted in human milk. In rats, [^{14}C]-radiolabel was detected in maternal milk after oral administration of 30 mg/kg/day and subsequently in gastrointestinal contents of pups. Milk radioactivity/plasma radioactivity ratio ranged between 2 and 4. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in nursing infants from dronedarone is unknown, women should be advised not to breast feed during treatment with dronedarone.

No studies have been performed in juvenile animals as the target population for the claimed indication is a predominantly elderly adult population.

Phototoxicity
The studies evaluating drug photosensitivity were conducted in the guinea-pig, which is widely accepted as a predictive model for man.

Dronedarone was shown to be only slightly phototoxic, i.e. phototoxic at high dose levels (from 100 mg/kg/day upwards), but not phototoxic at lower doses even following repeated administration. Whereas phototoxicity induced by amiodarone was still noted several weeks after treatment was stopped, the only change seen with dronedarone was the presence of a non-specific mild erythema (a reaction also observed in non treated animals during the course of the study) which persisted for at least 11 days after the last dronedarone administration. In addition, dronedarone was shown not to induce photoallergy, unlike amiodarone.

Immunotoxicity
In the specific immune function study, no primary or compound-related immunotoxicity was observed. No effect interpreted as an impairment of immune function was observed in the general toxicology studies; the thymic atrophy observed in some animals in different studies resulted from overall health deterioration and nonspecific stress (as indicated by several other histopathology findings involving other organs), commonly observed when animals are given very high dosages. Some slight increases in IgG and IgM levels were observed in rats only but these were not considered to be toxicologically relevant in the absence of other compound related effects on the immune system.

In conclusion, the extensive examination of immunotoxicity and immune function in animals has not demonstrated any compound related effect.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr MULTAQ®
Dronedarone Tablets
Read this carefully before you start taking **MULTAQ** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MULTAQ**.

What is MULTAQ used for?

MULTAQ is used in adults who have atrial fibrillation (abnormal heart rhythm which is rapid and irregular) that:

- lasts less than a week (paroxysmal atrial fibrillation) or
- lasts longer than a week (persistent atrial fibrillation).

It is used in people who currently have a normal heart rhythm or are going to be converted to a normal heart rhythm. It helps lower the chances of having to go into the hospital for atrial fibrillation.

How does MULTAQ work?

MULTAQ helps prevent or correct irregular heartbeats and other heart rhythm problems by blocking multiple channels in the heart. It works through several mechanisms, including blocking potassium, sodium, and calcium currents, and reducing adrenergic activity.

What are the ingredients in MULTAQ?

Medicinal ingredient: dronedarone hydrochloride

Non-medicinal ingredients: carnauba wax, colloidal anhydrous silica, crospovidone, hypromellose, lactose monohydrate, macrogol 6000, magnesium stearate, maize starch, poloxamer 407 and titanium dioxide

MULTAQ comes in the following dosage forms:

Tablets: 400 mg dronedarone (as dronedarone hydrochloride)

Do not use MULTAQ if:

- you are allergic to dronedarone or to any of the other ingredients in MULTAQ;
- you have or have a history of heart failure;
- you have permanent atrial fibrillation (an abnormal heart rhythm which is fast and irregular) and cannot be corrected by treatments;
- you have left ventricular systolic dysfunction (a weakness to a part of the heart that pumps oxygen-rich blood to the rest of the body);
- you have bradycardia (abnormally slow heart beat);
- you have any of the following heart problems and do not have a functional pacemaker:
    - second or third degree heart block (a type of irregular heart beat and rhythm);
    - complete bundle branch block (a type of abnormal heart rhythm caused by something blocking the electrical signal that causes your heart to beat);
    - distal block (the heart's electrical signals are blocked, making it hard for the heart to pump blood);

    - sinus node dysfunction (the heart's natural pacemaker is unable to create normal heartbeats at the normal rate).
- you have abnormal or unstable blood flow and blood pressure;
- you have a certain type of electrocardiogram (ECG) abnormality called QTc prolongation;
- you have liver or lung problems from using amiodarone;
- you take certain medicines that can change the amount of MULTAQ that gets into your body, such as:
    - ketoconazole;
    - itraconazole;
    - voriconazole;
    - cyclosporin;
    - clarithromycin;
    - ritonavir.
- you take certain medicines that can lead to torsade de pointes (a dangerous abnormal heart rhythm), such as:
    - phenothiazines;
    - antidepressants;
    - oral antibiotics;
    - certain medicines for abnormal heart rhythm or fast heartbeat.
- you have severe liver problems;
- you are pregnant or planning to become pregnant;
- you are breastfeeding or planning to breastfeed.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MULTAQ. Talk about any health conditions or problems you may have, including if you :

- are taking blood thinners (medicines that help prevent blood clots from forming in veins and arteries), such as dabigatran or rivaroxaban;
- have any heart problems;
- have low levels of potassium or magnesium in your blood;
- have liver problems;
- are 75 years of age or older.

Other warnings you should know about:

Taking MULTAQ may cause the following:

- **Heart problems:** MULTAQ can cause other heart problems such as heart failure. Your healthcare professional may monitor your heart throughout treatment. They will interpret the results and may have you stop taking MULTAQ. Talk to your healthcare professional if you:
    - have unexplained weight gain;
    - swelling in the legs, feet or arms;
    - increasing shortness of breath.

- **Liver problems:** MULTAQ can cause liver problems including liver injury. Your healthcare professional may monitor your liver throughout treatment. They will interpret the results and may have you stop taking MULTAQ. Talk to your healthcare professional right away if you have:
    - loss of appetite;
    - nausea, vomiting;

- fever, feeling unwell, unusual tiredness;
- pain or discomfort in the right upper stomach area;
- yellowing of the skin or whites of the eyes (jaundice);
- dark urine;
- itching.

Pregnancy and birth control:

- MULTAQ should not be used during pregnancy. Taking it during pregnancy may cause injury to your baby.
- If you are a woman who could become pregnant, your healthcare professional will ask you to do a pregnancy test before you start taking MULTAQ.
- You should use an effective birth control (contraception) method during treatment and for 7 days after your final dose of MULTAQ.
- Tell your healthcare professional right away if you become pregnant or think you are pregnant during treatment with MULTAQ.

Monitoring and testing: During your treatment with MULTAQ, your healthcare professional may perform tests, such as blood tests and electrocardiogram tests, to:

- monitor the health of your liver, kidneys and heart;
- determine how long it takes for your blood to clot.

Your healthcare professional will interpret your results and may stop your treatment with MULTAQ.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not take MULTAQ if you are taking:

- medicines that can change the amount of MULTAQ that gets into your body, such as:
  - ketoconazole and itraconazole, used to treat fungal infections;
  - ritonavir, used to treat HIV;
  - cyclosporin, used to treat organ rejection post-transplant;
  - clarithromycin, used to treat bacterial infections.
- medicines that can lead to torsade de pointe (a dangerous abnormal heart rhythm), such as:
  - phenothiazines, used to treat mental health problems and seizures;
  - medicines used to treat depression;
  - certain medicines used to treat bacterial infections;
  - medicines used to treat abnormal heart rhythms.

The following may also interact with MULTAQ:

- medicines known as beta-blockers used to treat high blood pressure (such as metoprolol and propranolol);
- medicines known as calcium antagonists used to help improve blood flow and reduce the workload on the heart (such as verapamil, diltiazem and nifedipine);
- digoxin, used to help the heart pump better and to control irregular heartbeats;

- erythromycin, used to treat bacterial infections in the body;
- medicines used to help prevent blood clots (such as dabigatran, rivaroxaban, edoxaban, apixaban, warfarin and other vitamin K antagonists);
- medicines known as P-glycoprotein (P-gp) substrates, including:
    - doxorubicin, used to treat cancer;
    - fexofenadine, used to relieve the symptoms of hay fever;
    - talinolol, used to treat high blood pressure.
- medicines known as potent CYP 3A4 inducers used to help breakdown and remove drugs (such as rifampicin, phenobarbital, carbamazepine and phenytoin);
- sirolimus and tacrolimus, used to help prevent organ rejection after transplant;
- medicines known as statins, used to lower high cholesterol in the blood (such as simvastatin, lovastatin, atorvastatin and pravastatin);
- theophylline, used to open up the airways in the lungs so it's easier to breathe;
- grapefruit juice. Do not drink grapefruit juice while you are taking MULTAQ;
- St John's Wort, an herbal compound commonly used to treat depression and mood disorders.

How to take MULTAQ:

- Take MULTAQ exactly as your healthcare professional tells you to. Do not stop taking MULTAQ without first talking to your healthcare professional.
- Take MULTAQ with a meal.

Usual dose:

Take one 400 mg tablet in the morning and one 400 mg tablet in the evening.

Overdose:

If you think you, or a person you are caring for, have taken too much MULTAQ, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you missed a dose of this medication, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using MULTAQ?

These are not all the possible side effects you may have when taking MULTAQ. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- digestive problems (such as diarrhea, nausea, vomiting, stomach pain and indigestion);
- feeling tired or weak;
- skin problems (such as redness, rash, itching, inflammation and eczema);
- change to or loss of your sense of taste.

Serious side effects and what to do about them			
Symptom / effects	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Bradycardia (abnormally slow heartbeat)		√	
UNKNOWN FREQUENCY			
Acute Kidney Failure (severe kidney problems): confusion; itchiness or rashes; puffiness in your face and hands; swelling in your feet or ankles; urinating less or not at all; weight gain.		√	
Allergic Reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			√
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat		√	
Congestive Heart Failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise		√	
Interstitial Lung Disease (diseases that inflame or scar lung tissue): shortness of breath when rest that gets worse with exertion, dry cough		√	
Liver Failure (serious disturbance of liver function, hepatic failure): yellow colour to skin, whites of the eyes (jaundice), bleeding easily, swollen abdomen, mental disorientation or confusion, sleepiness, coma		√	

Serious side effects and what to do about them			
Symptom / effects	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Liver Injury: pain in the right abdomen, fever, fatigue, weakness, nausea, vomiting, loss of appetite, yellowing of the skin or eyes, dark urine		√	
Prolongation of QT Interval (a heart rhythm condition): Irregular heartbeat, fainting, loss of consciousness, seizures		√	
Vasculitis (inflammation of the blood vessels): fever, fatigue, weight loss, muscle and joint pain, moss of appetite, numbness, weakness		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store MULTAQ at room temperature, between 15°C and 30°C.

Keep MULTAQ in its original packaging.

Keep out of reach and sight of children.

If you want more information about MULTAQ:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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