ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MULTAQ 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of dronedarone (as hydrochloride).

Excipient with known effect:

Each tablet also contains 41.65 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White, oblong shaped tablets, engraved with a double wave marking on one side and “4142”code on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MULTAQ is indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF). Due to its safety profile (see sections 4.3 and 4.4), MULTAQ should only be prescribed after alternative treatment options have been considered.
MULTAQ must not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.

4.2 Posology and method of administration

Treatment should be initiated and monitored only under specialist supervision (see section 4.4).
Treatment with dronedarone can be initiated in an outpatient setting.

Treatment with Class I or III antiarrhythmics (such as flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol, amiodarone) must be stopped before starting dronedarone.
There is limited information on the optimal timing to switch from amiodarone to dronedarone. 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 envisaged, this should be done under the supervision of a specialist (see sections 4.3 and 5.1).

Posology

The recommended dose is 400 mg twice daily in adults. It should be taken as:
- one tablet with the morning meal and
- one tablet with the evening meal.

Grapefruit juice should not be taken together with to dronedarone (see section 4.5).

If a dose is missed, patients should take the next dose at the regular scheduled time and should not double the dose.

Special populations

Elderly
Efficacy and safety were comparable in elderly patients who did not suffer from other cardiovascular diseases and younger patients. In patients ≥75years old, clinical signs of heart failure and ECG should be monitored on a regular basis when co-morbidities are present (see sections 4.3, 4.4 and 5.1). Although plasma exposure in elderly females was increased in a pharmacokinetic study conducted in healthy subjects, dose adjustments are not considered necessary (see sections 5.1 and 5.2).

Hepatic impairment
Dronedarone is contraindicated in patients with severe hepatic impairment because of the absence of data (see sections 4.3 and 4.4). No dose adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2).

Renal impairment
Dronedarone is contraindicated in patients with severe renal impairment (creatinine clearance (CrCl) <30 ml/min) (see section 4.3). No dose adjustment is required in other patients with renal impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of MULTAQ in children aged below 18 years of age have not yet been established. No data are available.

Method of administration

Oral use.
It is recommended to swallow the tablet whole with a drink of water during a meal. The tablet cannot be divided into equal doses.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Second- or third- degree atrio-ventricular 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)
- Bradycardia <50 beats per minute (bpm)
- Permanent AF with an AF duration ≥6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician
- Patients in unstable hemodynamic conditions
- History of, or current heart failure or left ventricular systolic dysfunction
- Patients with liver and lung toxicity related to the previous use of amiodarone
- Co-administration with potent cytochrome P 450 (CYP) 3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone and ritonavir (see section 4.5)
- Medicinal products inducing torsades de pointes such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, terfenadine and certain oral macrolides (such as erythromycin), Class I and III antiarrhythmics (see section 4.5)
- QTc Bazett interval ≥500 milliseconds
- Severe hepatic impairment
- Severe renal impairment (CrCl <30 ml/min)
- Co-administration with dabigatran

4.4 Special warnings and precautions for use

Careful monitoring during dronedarone administration is recommended by regular assessment of cardiac, hepatic and pulmonary function (see below). If AF reoccurs, discontinuation of dronedarone should be considered.
Treatment with dronedarone should be stopped during the course of treatment, in case the patient develops any of the conditions which would lead to a contraindication as mentioned in section 4.3.
Monitoring of co-administered medicinal products like digoxin and anti-coagulants is necessary.

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 heart failure in patients receiving dronedarone (see section 5.1). It is recommended to perform ECGs serially, at least every 6 months. If patients treated with dronedarone develop permanent AF, treatment with dronedarone should be discontinued.

Patients with history of, or current heart failure or left ventricular systolic dysfunction

Dronedarone is contraindicated in patients in unstable hemodynamic conditions, with history of, or current heart failure or left ventricular systolic dysfunction (see section 4.3).
Patients should be carefully evaluated for symptoms of Congestive Heart Failure. There have been spontaneously reported events of new or worsening heart failure during treatment with dronedarone. Patients should be advised to consult a physician if they develop or experience signs or symptoms of heart failure, such as weight gain, dependent oedema, or increased dyspnoea. If heart failure develops, treatment with dronedarone should be discontinued.
Patients should be followed for the development of left ventricular systolic dysfunction during treatment. If left ventricular systolic dysfunction develops, treatment with dronedarone should be discontinued.

Patients with coronary artery disease

In patients with coronary artery disease, clinical signs of heart failure and ECG should be regularly monitored to detect early signs of heart failure. In ESC and ACC/AHA/HRS guidelines dronedarone has a class IA recommendation in patients with paroxysmal/persistent AF and coronary artery disease.

Elderly

In elderly patients ≥75 years with multiple co-morbidities, clinical signs of heart failure and ECG should be monitored on a regular basis (see sections 4.2 and 5.1).

Women of child bearing potential and pregnancy

Dronedarone is not recommended during pregnancy and in women of childbearing potential not using contraception. Women of childbearing potential should use effective methods of contraception during treatment with dronedarone and for 7 days after the final dose. Prior to initiating dronedarone, the prescriber should confirm that women of childbearing potential are not pregnant (see section 4.6).

Liver injury

Hepatocellular liver injury, including life-threatening acute liver failure, has been reported in patients treated with dronedarone in the post-marketing setting. Liver function tests should be performed prior to initiation of treatment with dronedarone, after one week and after one month following initiation of treatment and then repeated monthly for six months, at months 9 and 12, and periodically thereafter.

If alanine aminotransferase (ALT) levels are elevated ≥3 × upper limit of normal (ULN), ALT levels should be re-measured within 48 to 72 hours. If ALT levels are confirmed to be ≥3 × ULN, treatment with dronedarone should be withdrawn. Appropriate investigation and close observation of patients should continue until normalisation of ALT.
Patients should immediately report any symptoms of potential liver injury (such as sustained new-onset abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine or itching) to their physician.

Management of plasma creatinine increase

An increase in plasma creatinine (mean increase 10 μmol/L) has been observed with dronedarone 400 mg twice daily in healthy subjects and in patients. In most patients this increase occurs early after treatment initiation and reaches a plateau after 7 days. It is recommended to measure plasma creatinine values prior to and 7 days after initiation of dronedarone. If an increase in creatininaemia is observed, serum creatinine should be re-measured after a further 7 days. If no further increase in creatininaemia is observed, this value should be used as the new reference baseline taking into account that this may be expected with dronedarone. If serum creatinine continues to rise then consideration should be given to further investigation and discontinuing treatment.
An increase in creatininaemia should not necessarily lead to the discontinuation of treatment with ACE inhibitors or Angiotensin II Receptors Antagonists (AIIRAs).
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 (see sections 4.3 and 4.4). It is recommended to monitor renal function periodically and to consider further investigations as needed.

Electrolytes imbalance

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

QT prolongation

The pharmacological action of dronedarone may induce a moderate QTc Bazett prolongation (about 10 msec), related to prolonged repolarisation. These changes are linked to the therapeutic effect of dronedarone and do not reflect toxicity. Follow up, including ECG (electrocardiogram), is recommended during treatment. If QTc Bazett interval is ≥500 milliseconds, dronedarone should be stopped (see section 4.3).
Based on clinical experience, dronedarone has a low pro-arrhythmic effect and has shown a decrease in arrhythmic death in the ATHENA study (see section 5.1).
However, proarrhythmic effects may occur in particular situations such as concomitant use with medicinal products favouring arrhythmia and/or electrolytic disorders (see sections 4.4 and 4.5).

Respiratory, thoracic and mediastinal disorders

Cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported in post-marketing experience. 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.

Interactions (see section 4.5)

Digoxin
Administration of dronedarone to patients receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with digoxin toxicity.

Clinical, ECG and biological monitoring is recommended, and digoxin dose should be halved. A synergistic effect on heart rate and atrioventricular conduction is also possible.

Beta-blockers and calcium antagonists
The co-administration of beta-blockers or calcium antagonists with depressant effect on sinus and atrio-ventricular node should be undertaken with caution. These medicinal products should be initiated at low dose and up titration should be done only after ECG assessment. In patients already on calcium antagonists or beta blockers at time of dronedarone initiation, an ECG should be performed and the dose should be adjusted if needed.

Vitamin K antagonists
Patients should be appropriately anti-coagulated as per clinical AF guidelines. International Normalised Ratio (INR) should be closely monitored after initiating dronedarone in patients taking vitamin K antagonists as per their label.

Potent CYP3A4 inducers
Potent CYP3A4 inducers such as rifampicin, phenobarbital, carbamazepine, phenytoin or St John's Wort are not recommended.

Statins
Statins should be used with caution. Lower starting dose and maintenance doses of statins should be considered and patients monitored for clinical signs of muscular toxicity.

Grapefruit juice
Patients should be warned to avoid grapefruit juice beverages while taking dronedarone.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Dronedarone is primarily metabolised by CYP 3A4 (see section 5.2). Therefore, inhibitors and inducers of CYP 3A4 have the potential to interact on dronedarone.
Dronedarone is a moderate inhibitor of CYP 3A4, a mild inhibitor of CYP 2D6 and a potent inhibitor of P-glycoproteins (P-gp). Dronedarone has, therefore, the potential to interact on medicinal products substrates of P-glycoproteins, CYP 3A4 or CYP 2D6. Dronedarone and/or its metabolites also have been shown to inhibit transport proteins of the Organic Anion Transporter (OAT), Organic Anion Transporting Polypeptide (OATP) and Organic Cation Transporter (OCT) families *in vitro*.
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.

Medicinal products inducing torsades de pointes

Medicinal products inducing torsades de pointes such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, certain oral macrolides (such as erythromycin), terfenadine and Class I and III antiarrhythmics are contraindicated because of the potential risk of proarrhythmia (see section 4.3).
In patients already taking beta-blockers at time of dronedarone initiation, an ECG should be performed and the dose of beta-blocker should be adjusted if needed (see section 4.4).
Clinical, ECG and biological monitoring is recommended, and digoxin dose should be halved (see section 4.4).

Effect of other medicinal products on dronedarone

Potent CYP 3A4 inhibitors
Repeated doses of 200 mg ketoconazole daily resulted in a 17-fold increase in dronedarone exposure. Therefore, concomitant use of ketoconazole as well as other potent CYP 3A4 inhibitors such as itraconazole, voriconazole, pozaconazole, ritonavir, telithromycin, clarithromycin or nefazodone is contraindicated (see section 4.3).

Moderate/weak CYP 3A4 inhibitors

Erythromycin
Erythromycin, an oral macrolide, may induce torsades de pointes and, as such, is contraindicated (see section 4.3). 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.

Calcium antagonists
Calcium antagonists, diltiazem and verapamil, are substrates and/or moderate inhibitors of CYP 3A4. Moreover, due to their heart rate-lowering properties, verapamil and diltiazem 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. 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 studies, 13% of patients received calcium antagonists concomitantly with dronedarone. There was no increased risk of hypotension, bradycardia and heart failure.
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 medicinal products 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 calcium antagonist dose should be adjusted if needed (see section 4.4).

Other moderate/weak CYP 3A4 Inhibitors
Other moderate inhibitors of CYP3A4 are also likely to increase dronedarone exposure.

CYP 3A4 inducers
Rifampicin (600 mg once daily) decreased dronedarone exposure by 80% with no major change on its active metabolite exposure. Therefore, co-administration of rifampicin and other potent CYP 3A4 inducers such as phenobarbital, carbamazepine, phenytoin or St John's Wort is not recommended as they decrease dronedarone exposure.

MAO inhibitors
In an *in vitro* study MAO contributed to the metabolism of the active metabolite of dronedarone. The clinical relevance of this observation is not known (see sections 4.4 and 5.2).

Effect of dronedarone on other medicinal products

Interaction with medicinal products metabolised by CYP 3A4

Dabigatran
When dabigatran etexilate 150 mg once daily was co-administered with dronedarone 400 mg twice daily, the dabigatran AUC0-24, and C_{max} were increased by 100% and 70%, respectively. No clinical data are available regarding the co-administration of these medicinal products in AF patients. Their co-administration is contraindicated (see section 4.3).

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 exposure of lovastatin within the same range as simvastatin acid. There was a weak interaction between dronedarone and atorvastatin (which resulted in a mean 1.7-fold increase in atorvastatin exposure). There was a weak interaction between dronedarone and statins transported by OATP, such as rosuvastatin (which resulted in a mean 1.4-fold increase in rosuvastatin exposure).
In clinical trials, there was no evidence of safety concerns when dronedarone was co-administered with statins metabolised by CYP 3A4. However, spontaneously reported cases of rhabdomyolysis when dronedarone was given in combination with a statin (simvastatin in particular) have been reported, and, therefore, concomitant use of statins 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 (see section 4.4).

Calcium antagonists
The interaction of dronedarone on calcium antagonists is described above (see section 4.4).

Immunosuppressants
Dronedarone could increase plasma concentrations of immunosuppressants (tacrolimus, sirolimus, everolimus and cyclosporine). Monitoring of their plasma concentrations and appropriate dose adjustment is recommended in case of coadministration with dronedarone.

Oral contraceptives
No decreases in ethinylestradiol and levonorgestrel were observed in healthy subjects receiving dronedarone (800 mg twice daily) concomitantly with oral contraceptives.

Interaction with medicinal products metabolised by CYP 2D6

Beta-blockers
Sotalol must be stopped before starting dronedarone (see sections 4.2 and 4.3). Beta-blockers that are metabolised 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 metabolisers). In clinical studies, 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 concomitantly with dronedarone. These medicinal products should be initiated at low dose and up-titration should be done only after ECG assessment. In patients already taking beta-blockers at time of dronedarone initiation, an ECG should be performed and the beta-blocker dose should be adjusted if needed (see section 4.4).

Antidepressants
Since dronedarone is a weak inhibitor of CYP 2D6 in humans, it is predicted to have limited interaction on antidepressant medicinal products metabolised by CYP 2D6.

Interaction with P-gp substrates

Digoxin
Dronedarone (400 mg twice daily) increased digoxin exposure by 2.5-fold by inhibiting P-gp transporter. Moreover, digitalis has the potential to interact with dronedarone from a pharmacodynamic point of view. A synergistic effect on heart rate and atrio-ventricular conduction is possible. In clinical studies, increased levels of digitalis and/or gastrointestinal disorders indicating digitalis toxicity were observed when dronedarone was co-administered with digitalis.
The digoxin dose should be reduced by approximately 50%, serum levels of digoxin should be closely monitored and clinical and ECG monitoring is recommended.

Interaction with medicinal products metabolised by CYP 3A4 and P-gp

Rivaroxaban
Dronedarone is likely to increase the exposure of rivaroxaban (a CYP3A4 and P-gp substrate) and consequently concomitant use may increase the risk of bleedings. Concomitant use of rivaroxaban and dronedarone is not recommended.

Apixaban
Dronedarone may increase the exposure of apixaban (a CYP3A4 and P-gp substrate). However, no dose adjustment for apixaban is required when co-administered with agents that are not strong inhibitors of both CYP3A4 and P-gp, such as dronedarone.

Edoxaban
In *in vivo* studies edoxaban (a CYP3A4 and P-gp substrate) exposure was increased when administered with dronedarone. The edoxaban dose should be reduced according to the edoxaban label recommendations.

Interaction with warfarin and losartan (CYP 2C9 substrates)

Warfarin and other vitamin K antagonists
Dronedarone (600 mg twice daily) increased by 1.2-fold S-warfarin with no change in R-warfarin and only a 1.07 increase in International Normalised Ratio (INR).
However, clinically significant INR elevations (≥5) usually within 1 week after starting dronedarone were reported in patients taking oral anticoagulants. Consequently, INR should be closely monitored after initiating dronedarone in patients taking vitamin K antagonists as per their label.

Losartan and other Angiotensin II Receptor Antagonists (AIIRAs)
No interaction was observed between dronedarone and losartan and an interaction between dronedarone and other AIIRAs is not expected.

Interaction with theophylline (CYP 1A2 substrate)
Dronedarone 400 mg twice daily does not increase the steady state theophylline exposure.

Interaction with metformin (OCT1 and OCT2 substrate)
No interaction was observed between dronedarone and metformin, an OCT1 and OCT2 substrate.

Interaction with omeprazole (CYP 2C19 substrate)
Dronedarone does not affect the pharmacokinetics of omeprazole, a CYP 2C19 substrate.

Interaction with clopidogrel
Dronedarone does not affect the pharmacokinetics of clopidogrel and its active metabolite.

Other information
Pantoprazole (40 mg once daily), a medicinal product which increases gastric pH without any effect on cytochrome P450, did not interact significantly on dronedarone pharmacokinetics.

Grapefruit juice (CYP 3A4 inhibitor)

Repeated doses of 300 ml of grapefruit juice 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 (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of child bearing potential and pregnancy

MULTAQ is not recommended during pregnancy and in women of childbearing potential not using contraception. There are no or limited data from the use of dronedarone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

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

Prior to initiating MULTAQ, the prescriber should confirm that women of childbearing potential are not pregnant.

Breast-feeding

It is unknown whether dronedarone and its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dronedarone and its metabolites in milk. A risk to the newborns/infants cannot be excluded. Women should be advised not to breastfeed during treatment with MULTAQ and for 7 days (about 5 half-lives) after the final dose.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from MULTAQ therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Dronedarone was not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

MULTAQ has no or negligible influence on the ability to drive and use machines. However, ability to drive and use machines may be affected by adverse reactions such as fatigue.

4.8 Undesirable effects

Summary of the safety profile

Assessment of intrinsic factors such as gender or age on the incidence of any treatment emergent adverse reactions showed an interaction for gender (female patients) for the incidence of any adverse reactions and for serious adverse reactions.

In clinical studies, 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 dronedarone 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 diarrhoea (9%), nausea (5%) and vomiting (2%), fatigue and asthenia (7%).

Tabulated list of adverse reactions

The safety profile of dronedarone 400 mg twice daily in patients with atrial fibrillation (AF) or atrial flutter (AFL) is based on 5 placebo controlled studies, in which a total of 6,285 patients were randomised (3,282 patients received dronedarone 400 mg twice daily, and 2,875 received placebo). The mean exposure across studies was 13 months. In ATHENA study, the maximum follow-up was 30 months. Some adverse reactions were also identified during post-marketing surveillance.
Adverse reactions are presented by system organ class.
Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from

the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions

System organ class	**Very Common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)
Immune system disorders				Anaphylactic reactions including angioedema
Nervous system disorders			Dysgeusia	Ageusia
Cardiac disorders	Congestive heart failure (see below)	Bradycardia (see sections 4.3 and 4.4)		
Vascular disorders				Vasculitis, including leukocytoclastic vasculitis
Respiratory, thoracic and mediastinal disorders			Interstitial lung disease including pneumonitis and pulmonary fibrosis (see below)	
Gastrointestinal disorders		Diarrhoea Vomiting Nausea Abdominal pain Dyspepsia		
Hepatobiliary disorders		Liver function test abnormalities		Hepatocellular liver injury, including life-threatening acute liver failure (see section 4.4)
Skin and subcutaneous tissue disorders		Rashes (including generalised, macular, maculo-papular) Pruritus	Erythemas (including erythema and rash erythematous) Eczema Photosensitivity reaction Dermatitis allergic Dermatitis	
General disorders and administration site conditions		Fatigue Asthenia		
Investigations	Blood creatinine increased*			

System organ class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
	QTc Bazett prolonged #			

* ≥10% five days after treatment initiation (see section 4.4)
# >450 msec in male >470 msec in female (see section 4.4)

Description of selected adverse reactions

Congestive heart failure
In the 5 placebo controlled studies, CHF occurred in the dronedarone group with rates comparable with placebo (very commonly, 11.2% versus 10.9%). This rate should be considered in the context of the underlying elevated incidence of CHF in AF patients. Cases of CHF have also been reported in post-marketing experience (frequency not known) (see section 4.4).

Interstitial lung disease including pneumonitis and pulmonary fibrosis
In the 5 placebo controlled studies, 0.6% of patients in the dronedarone group had pulmonary events versus 0.8% of patients receiving placebo. Cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported in post-marketing experience (frequency not known). A number of patients had been previously exposed to amiodarone (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

It is not known whether dronedarone 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cardiac therapy, antiarrhythmics class III, ATC code: C01BD07

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 IK(Ach), IKur, IKr, IKs) 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 antagonises adrenergic activities (Class II).

Pharmacodynamic properties

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 on QTc-intervals, and with no change in HV- and QRS- intervals. It increases effective refractory periods (ERP) of the atrium, atrio-ventricular node, and ventricular ERP was slightly prolonged with a minimal degree of reverse frequency 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, in coronary arteries (related to the activation of the nitric oxide pathway) and in peripheral arteries.
Dronedarone displays indirect antiadrenergic effects and partial antagonism to adrenergic stimulation. It reduces alpha-adrenergic blood pressure response to epinephrine and beta1 and beta2 responses to isoproterenol.

Clinical efficacy and safety

Reduction of risk of AF-related hospitalisation
The efficacy of dronedarone in the reduction of risk of AF-related hospitalisation was demonstrated in patients with AF or a history of AF and additional risk factors in the ATHENA multicenter, multinational, double blind, and randomised 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 who received amiodarone within 4 weeks prior to randomisation were not included. Patients could be in AF/AFL or in sinus rhythm after spontaneous conversion or following any procedures.

Four thousand six hundred and twenty eight (4,628) patients were randomised and treated for up to 30 months maximum (median follow-up: 22 months) with either dronedarone 400 mg twice daily (2,301 patients) or placebo (2,327 patients), in addition to conventional therapy including beta-blockers (71%), ACE inhibitors or AIIRAs (69%) digitalis (14%), calcium antagonists (14%), statins (39%), oral anticoagulants (60%), chronic antiplatelet 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.
Patients ranged in age from 23 to 97 years and 42% were over 75 years old. Forty seven percent (47%) of patients were female and a majority was Caucasian (89%).

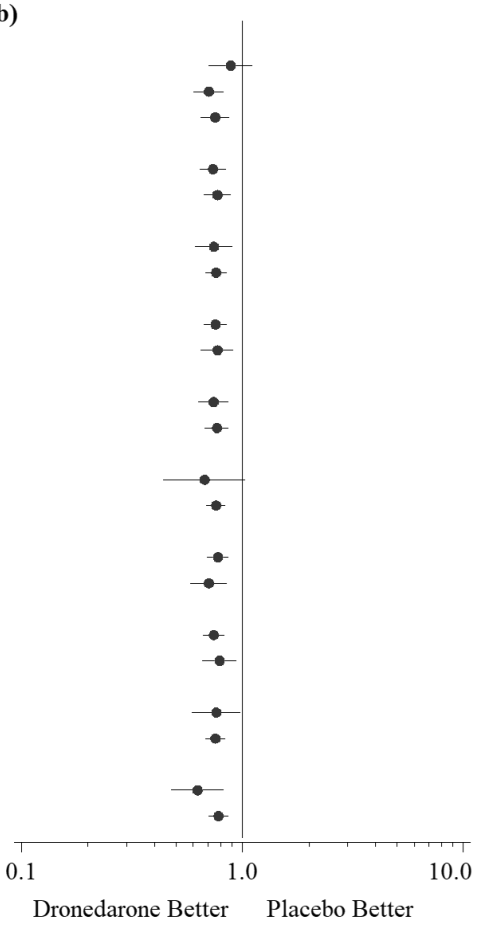
The majority had hypertension (86%) and structural heart disease (60%) (including coronary artery disease: 30%; congestive heart failure (CHF): 30%; LVEF<45%: 12%).
Twenty five percent (25%) had AF at baseline.

Dronedarone reduced the incidence of cardiovascular hospitalisation or death from any cause by 24.2% when compared to placebo ($p<0.0001$).

The reduction in cardiovascular hospitalisation or death from any cause was consistent in all subgroups, irrespective of baseline characteristics or medicinal products (ACE inhibitors or AIIRAs; beta-blockers, digitalis, statins, calcium antagonists, diuretics) (see figure 1).

Figure 1 - Relative risk (dronedarone 400 mg twice daily versus placebo) - first cardiovascular hospitalisation 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

Similar results were obtained on the incidence of cardiovascular hospitalisation with a risk reduction of 25.5% (p <0.0001).
During the course of the study, the number of deaths from any cause was comparable between the dronedarone (116/2,301) and placebo (139/2,327) groups.

Maintenance of sinus rhythm
In EURIDIS and ADONIS, a total of 1,237 patients with a prior episode of AF or AFL were randomised in an outpatient setting and treated with either dronedarone 400 mg twice daily (n = 828) or placebo (n = 409) on top of conventional therapies (including oral anticoagulants, beta-blockers, ACE inhibitors or AIIRAs, 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. In patients who were taking amiodarone, an ECG was to be performed about 4 hours after the first administration to verify good tolerability. Other antiarrhythmic medicinal products had to be withdrawn for at least 5 plasma half-lives prior to the first administration.
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, dronedarone consistently delayed the time to first recurrence of AF/AFL (primary endpoint). As compared to placebo, dronedarone lowered the risk of first AF/AFL recurrence during the 12-month study period

by 25% (p = 0.00007). The median time from randomised to first AF/AFL recurrence in the dronedarone group was 116 days, i.e. 2.2-fold longer than in the placebo group (53 days).

The DIONYSOS study compared the efficacy and safety of dronedarone (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. Patients ranged in age from 28 to 90 years, 49% were more than 65 years old. 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 dronedarone 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%).

Patients with symptoms of heart failure at rest or with minimal exertion within the previous month or who were hospitalised for heart failure during the previous month
The ANDROMEDA study was conducted in 627 patients with left ventricular dysfunction, hospitalised with new or worsening heart failure and who had had at least one episode of shortness of breath on minimal exertion or at rest (NYHA class III or IV) or paroxysmal nocturnal dyspnoea within the month before admission. Patients ranged in age from 27 to 96 years, 68% were more than 65 years old. The study was stopped prematurely due to an observed imbalance of deaths in the dronedarone group [n = 25 versus 12 (placebo), p = 0.027] (see sections 4.3 and 4.4).

Patients with permanent atrial fibrillation
The PALLAS study was a randomised placebo-controlled study investigating the clinical benefit of dronedarone 400 mg BID on top of standard therapy in patients with permanent atrial fibrillation and additional risk factors (patients with congestive heart failure ~ 69%, coronary heart disease ~ 41%, prior stroke or TIA ~ 27%; LVEF ≤40% ~ 20.7% and patients ≥75 years with hypertension and diabetes ~ 18%). The study was prematurely stopped after randomization of 3,149 patients (placebo = 1,577; dronedarone = 1,572) due to the significant increase in heart failure (placebo = 33; dronedarone = 80; HR = 2.49 (1.66-3.74)]; stroke [placebo = 8; dronedarone = 17; HR = 2.14 (0.92-4.96)] and cardiovascular death [placebo = 6; dronedarone = 15; HR = 2.53 (0.98-6.53)] (see sections 4.3 and 4.4).

5.2 Pharmacokinetic properties

Absorption

Following oral administration in fed condition, 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. 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 99.7% and 98.5% respectively and is not saturable. Both compounds bind mainly to albumin. After intravenous administration the volume of distribution at steady state (Vss) ranges from 1,200 to 1,400 L.

Biotransformation

Dronedarone is extensively metabolised, mainly by CYP 3A4 (see section 4.5). 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 (see section 4.5).
The N-debutyl metabolite exhibits pharmacodynamic activity but is 3 to 10-times less potent than dronedarone. This metabolite contributes to the pharmacological activity of dronedarone in humans.

Elimination

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 intravenous 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 AF is consistent with that in healthy subjects. Gender, age and weight are factors that influence the pharmacokinetics of dronedarone. Each of these factors has a limited influence on dronedarone.

Gender
In female patients, dronedarone exposures and its N-debutyl metabolite exposure are on average 1.3- to 1.9-fold 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 years of age and over. In patients aged 65 years of age and over, dronedarone exposures are 23% higher in comparison with patients aged below 65 years of age.

Hepatic impairment
In subjects with moderate hepatic impairment, dronedarone unbound exposure is increased by 2-fold. The mean exposure of the N-debutyl metabolite is decreased by 47% (see section 4.2).
The effect of severe hepatic impairment on the pharmacokinetics of dronedarone was not assessed (see section 4.3).

Renal impairment
The effect of renal impairment on dronedarone pharmacokinetics has not been evaluated in a specific study. Renal impairment is not expected to modify the pharmacokinetics of dronedarone because no unchanged compound was excreted in urine and only approximately 6% of the dose was excreted in urine as metabolites (see section 4.2).

5.3 Preclinical safety data

Dronedarone had no genotoxic effects, based on one *in vivo* micronucleus test in mice and four *in vitro* tests.
In 2-year oral carcinogenicity studies, the highest dronedarone dose administered for 24 months was 70 mg/kg/day in rats 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). Hemangiomas are not precancerous changes and do not transform into malignant hemangiosarcomas in either animals or man. None of these observations was considered relevant for humans.

In 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.

Dronedarone caused marked effects on embryo-foetal development at high doses in rats, such as increased post-implantation losses, reduced foetal and placental weights, and external, visceral and skeletal malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose (E464)
Maize starch
Crospovidone (E1202)
Poloxamer 407
Lactose monohydrate
Colloidal anhydrous silica
Magnesium stearate (E572)

Tablet coat

Hypromellose (E464)
Macrogol 6000
Titanium dioxide (E171)
Carnauba wax (E903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

- Opaque PVC/Aluminium blister in packs of 20, 50 and 60 film-coated tablets
- Opaque PVC/Aluminium perforated unit dose blister in packs of 100x1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/591/001 - cartons of 20 film-coated tablets
EU/1/09/591/002 - cartons of 50 film-coated tablets
EU/1/09/591/003 - cartons of 60 film-coated tablets
EU/1/09/591/004 - cartons of 100 x 1 film-coated tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 November 2009
Date of latest renewal: 19 September 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Sanofi Winthrop Industrie
1 rue de la Vierge
Ambarès et Lagrave
F-33565 Carbon Blanc Cedex
France

Sanofi-Aventis Deutschland GmbH
Brüningstrasse 50
Industriepark Höchst,
D-65926 Frankfurt
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The marketing authorisation holder shall ensure that Health care professionals who intend to prescribe or dispense MULTAQ are provided or have access to the most recent version of SmPC and MULTAQ Prescriber guide.

The content and format of the MULTAQ Prescriber guide, together with the communication and distribution plan should be agreed with the National Competent Authority in each Member State prior to distribution.

The following risks:

- Heart Failure (including use in patients with unstable hemodynamic conditions with history of, or current heart failure or left ventricular systolic dysfunction, and pre-renal azotemia)
- Use in Permanent atrial fibrillation defined as an AF duration ≥6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician
- Pulmonary-interstitial lung disease (ILD)
- Hepatotoxicity

are concerned by the additional minimization measures.

The educational material is a Prescriber Guide to:

- Screen patients before treatment initiation
  - Contra indication of Permanent Atrial fibrillation
  - Contra indication of history, or current heart failure or left ventricular systolic dysfunction (LVSD)
  - Prevention of drug-drug interaction
  - Liver, lung and renal safety of use.
- Monitor patients during treatment and discontinue dronedarone when required
  - ECG
  - Cardiac clinical symptoms
  - Drug interaction
  - Liver, pulmonary, coagulation and renal function tests
- Counsel patients about its use
  - Educate patients on symptoms
  - Encourage reporting to Pharmacovigilance

The Prescriber Guide should display information to help physician assess whether the patient is eligible for MULTAQ prescription and whether the patient remains within the prescribing information.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

MULTAQ 400 mg film-coated tablets
dronedarone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 400 mg dronedarone (as hydrochloride).

3. LIST OF EXCIPIENTS

Also contains: lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/591/001 20 film-coated tablets
EU/1/09/591/002 50 film-coated tablets
EU/1/09/591/003 60 film-coated tablets
EU/1/09/591/004 100x1 film-coated tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MULTAQ 400 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

MULTAQ 400 mg tablets
dronedarone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

MULTAQ 400 mg film-coated tablets
dronedarone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What MULTAQ is and what it is used for
2. What you need to know before you take MULTAQ
3. How to take MULTAQ
4. Possible side effects
5 How to store MULTAQ
6. Contents of the pack and other information

1. What MULTAQ is and what it is used for

MULTAQ contains an active substance named dronedarone. It belongs to a group of medicines called anti-arrhythmics that help regulate your heart beat.

MULTAQ is used if you have a problem with your heart rhythm (your heart beats out of time - atrial fibrillation) and through a treatment called cardioversion has changed your heartbeat back to normal rhythm.
MULTAQ prevents repetition of your problem of irregular heart rhythm. MULTAQ is used only in adults.

Your doctor will consider all available treatment options before prescribing MULTAQ to you.

2. What you need to know before you take MULTAQ

Do not take MULTAQ:

- if you are allergic to dronedarone or to any of the other ingredients of this medicine (listed in section 6),
- if you have a problem with the nerves in your heart (heart block). Your heart might beat very slowly or you may feel dizzy. If you have had a pacemaker fitted for this problem, you can use MULTAQ,
- if you have a very slow heart beat (less than 50 beats a minute),
- if your ECG (electrocardiogram) shows a heart problem called “prolonged QT corrected interval” (this interval is more than 500 milliseconds),
- if you have a type of atrial fibrillation called permanent atrial fibrillation (AF). In permanent AF, the AF has been present for a long time (at least during 6 months) and a decision has been made not to change back your heart rhythm to atrial normal rhythm with a treatment called cardioversion,
- if you have instability (drops) in your blood pressure which can lead to inadequate arterial blood flow to your organs,

- if you have or had a problem where your heart cannot pump the blood round your body as well as it should (condition called heart failure). You may have swollen feet or legs, trouble breathing when lying down or sleeping, or shortness of breath when moving around,
- if the percentage of blood leaving your heart each time it contracts is too low (condition called left ventricular dysfunction),
- if you took amiodarone (another antiarrhythmic medicine) previously and experienced lung or liver problems,
- if you take medicines for infection (including fungal infection or AIDS), allergies, heart beat problems, depression, after a transplant (see section below on "Other medicines and MULTAQ". This will give you more details on exactly what medicines you cannot take with MULTAQ),
- if you have a severe liver problem,
- if you have a severe kidney problem,
- if you take dabigatran (see section below on "Other medicines and MULTAQ").

If any of the above apply to you, do not take MULTAQ.

Warnings and precautions
Talk to your doctor or pharmacist before taking MULTAQ if
- you have a problem that gives you a low level of potassium or magnesium in your blood. This problem should be corrected before starting treatment with MULTAQ,
- you are more than 75 years old,
- you have a condition when the vessel that supplies blood to heart muscle becomes hardened and narrowed (coronary artery disease).

While taking MULTAQ, tell your doctor if
- your atrial fibrillation becomes permanent while you are taking MULTAQ. You should stop taking MULTAQ,
- you have swollen feet or legs, trouble breathing when lying down or sleeping, shortness of breath when moving around, or weight increase (which are signs and symptoms of heart failure),
- tell your doctor immediately if you develop any of these signs and symptoms of liver problems: stomach (abdominal) area pain or discomfort, loss of appetite, nausea, vomiting, yellowing of the skin or the whites of the eyes (jaundice), unusual darkening of the urine, fatigue (especially in association with other symptoms listed above), itching,
- you have breathlessness or non-productive cough. Tell your doctor, he/she will check your lung.

If this applies to you (or you are not sure), please talk to your doctor or pharmacist before taking MULTAQ.

Heart, lung and blood tests
While you are taking MULTAQ, your doctor may perform tests to check your medical condition and how the medicine is working for you.
- Your doctor may look at your heart's electrical activity using an ECG (electrocardiogram) machine.
- Your doctor will order blood tests to check your liver function before you start taking MULTAQ and during treatment.
- If you are taking some medicines against blood clot formation such as warfarin, your doctor will order a blood test called INR to check how well your medicine is working.
- Your doctor may also do other blood tests. The results of one of the blood tests to check kidney function (blood creatinine levels) may be changed by MULTAQ. Your doctor will take this into account when checking your blood levels and will use another reference of the "normal" value of blood creatinine.
- Your doctor may check your lungs.

In some cases, MULTAQ treatment may need to be stopped.

Please tell any other person who checks your blood that you are taking MULTAQ.

Children and adolescents
MULTAQ is not recommended in children and adolescents below 18 years of age.

Other medicines and MULTAQ
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Your doctor may recommend that you use a medicine against blood clot formation according to your condition.

MULTAQ and some other medicines can affect each other and cause serious side effects. Your doctor may change the dose of any other medicines you are taking.

You must not take any of the following with MULTAQ:
- other medicines used to control an irregular or fast heart beat such as flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol, amiodarone,
- some medicines for fungal infections such as ketoconazole, voriconazole, itraconazole or posaconazole,
- some medicines for depression called tricyclic antidepressants,
- some tranquilising medicines called phenothiazines,
- bepridil for chest pain caused by heart disease,
- telithromycin, erythromycin, or clarithromycin (antibiotics for infections),
- terfenadine (a medicine for allergies),
- nefazodone (a medicine for depression),
- cisapride (a medicine for food and acid reflux from your stomach to your mouth),
- ritonavir (a medicine for AIDS infection),
- dabigatran (a medicine for prevention of blood clot formation).

You must tell your doctor or pharmacist if you are taking any of the following medicines:
- other medicines for high blood pressure, for chest pain caused by heart disease, or other heart problems, such as verapamil, diltiazem, nifedipine, metoprolol, propranolol or digoxin,
- some medicines for reducing the cholesterol in your blood (such as simvastatin, lovastatin, atorvastatin, or rosuvastatin),
- some medicines against blood clot formation such as warfarin, rivaroxaban, edoxaban and apixaban.
- some medicines for epilepsy called phenobarbital, carbamazepine or phenytoin,
- sirolimus, tacrolimus, everolimus and cyclosporine (used after a transplant),
- St John’s Wort - a herbal medicine for depression,
- rifampicin - for tuberculosis.

MULTAQ with food and drink
Do not drink grapefruit juice while taking MULTAQ. It can increase the blood levels of dronedarone and may increase your chance of getting side effects.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- If you are a woman able to have children, the doctor will do a pregnancy test before you start the treatment with MULTAQ.
- MULTAQ is not recommended if you are pregnant or you think you may be pregnant. Do not take MULTAQ if you are a woman able to have children and you are not using a reliable contraceptive method.
- Use effective birth control (contraception) during treatment and for 7 days after the final dose of MULTAQ.

- Stop taking your tablets and talk to your doctor straight away if you get pregnant while taking MULTAQ.
- It is not known if MULTAQ passes into your breast milk. You and your doctor should decide if you will take MULTAQ or breastfeed. Do not breastfeed during treatment with MULTAQ and for 7 days after the final dose.

Driving and using machines
MULTAQ does not usually affect your ability to drive or use machine. However, your ability to drive and use machines may be affected by side effects such as tiredness.

MULTAQ contains lactose
Lactose is a type of sugar. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take MULTAQ

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
Treatment with MULTAQ will be overseen by a doctor who is experienced in the treatment of heart disease.

If you need to change from amiodarone (another medicine for irregular heart beat) to MULTAQ, your doctor can provide special recommendations, for example pausing amiodarone before switching. Tell your doctor about all the medicines you take.

How much to take
The usual dose is one 400 mg tablet twice a day. Take:
- one tablet during your morning meal and
- one tablet during your evening meal.

If you think that your medicine is too strong or too weak, talk to your doctor or pharmacist.

Taking this medicine
Swallow the tablet whole with a drink of water during a meal. The tablet cannot be divided into equal doses.

If you take more MULTAQ than you should
Contact immediately your doctor or the nearest emergency department or hospital. Take the medicine pack with you.

If you forget to take MULTAQ
Do not take a double dose to make up for a forgotten tablet. Take the next dose when you are normally due to take it.

If you stop taking MULTAQ
Do not stop taking this medicine without first talking to your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported with this medicine:

Talk to your doctor straight away, if you notice any of the following serious side effects – you may need urgent medical assistance

Very common (may affect more than 1 in 10 people)

- Problem where your heart does not adequately pump the blood round your body as well as it should (congestive heart failure) In clinical studies, this side effect was observed at a similar rate in patients receiving MULTAQ and in patients receiving placebo. Signs include swollen feet or legs, trouble breathing when lying down or sleeping, shortness of breath when moving around, or weight increase.

Common (may affect up to 1 in 10 people)

- Diarrhoea, vomiting when excessive as it can lead to kidney problems.
- Slow heart beat.

Uncommon (may affect up to 1 in 100 people)

- Inflammation of the lungs (including scarring and thickening of the lungs). Signs include breathlessness or non-productive cough.

Rare (may affect up to 1 in 1,000 people)

- Liver problems including life threatening liver failure. Signs include stomach (abdominal) area pain or discomfort, loss of appetite, nausea, vomiting, yellowing of the skin or the whites of the eyes (jaundice), unusual darkening of the urine, fatigue (especially in association with other symptoms listed above), itching.
- Allergic reactions, including swelling of the face, lips, mouth, tongue or throat.

Other side effects include:

Very Common

- changes in the results of one blood test: your blood creatinine level,
- changes in your ECG (electrocardiogram) called QTc Bazett prolonged.

Common

- problems with your digestive system such as indigestion, diarrhoea, nausea, vomiting and stomach pain,
- feeling tired,
- skin problems such as rash or itching,
- change in the results of blood tests used to check your liver function.

Uncommon

- other skin problems such as redness of the skin or eczema (redness, itching, burning or blistering),
- your skin being more sensitive to the sun,
- change in how things taste.

Rare

- losing your sense of taste,
- inflammation of blood vessels (vasculitis including leukocytoclastic vasculitis).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store MULTAQ

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the blister and carton after "EXP." The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not use this medicine if you notice any visible sign of deterioration (see section 6).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What MULTAQ contains

- The active substance is dronedarone.
  Each film-coated tablet contains 400 mg of dronedarone (as hydrochloride).
- The other ingredients in the tablet core are hypromellose (E464), maize starch, crospovidone (E1202), poloxamer 407, lactose monohydrate (see section 2 under 'MULTAQ contains lactose'), colloidal anhydrous silica, magnesium stearate (E572).
- The other ingredients in the tablet coat are hypromellose (E464), macrogol 6000, titanium dioxide (E171), carnauba wax (E903).

What MULTAQ looks like and content of the pack
MULTAQ is a white, oval, film-coated tablet (tablet) with a double wave marking on one side and "4142" on the other side.

MULTAQ film-coated tablets are supplied in packs of 20, 50, 60 tablets in opaque PVC and aluminium blisters and 100x1 tablets in opaque PVC and aluminium perforated unit dose blisters. Not all pack size may be marketed.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.