European Medicines Agency
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Withdrawal Public Assessment Report

Of the Marketing Authorisation Application for

Multaq
(Dronedarone)

This Withdrawal Public Assessment Report is based on the Day 120 assessment report, which is the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the marketing authorisation application. This Withdrawal Public Assessment Report does not include all available information on the product as the CHMP assessment of the applicant's responses to Outstanding Issues raised by CHMP was still ongoing.
It should therefore be read in conjunction with the Questions and Answers Document on the withdrawal of the marketing application for this product, which provides an overview on all available information on the product at the time of the Applicant's withdrawal.

This product was later resubmitted to the EMEA. See here for information on the outcome of the resubmission.

EMEA/H/C/676

Applicant: sanofi-aventis

Start of the procedure:	20 July 2005
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LIST OF ABBREVIATIONS

ADME	Absorption, distribution, metabolism and excretion
AERP	Atrial effective refractory period
AF	Atrial fibrillation
AH	Atrium-His
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
AP	Action potential
APA	Action potential amplitude
APD	Action potential duration
APD30, APD50, APD70 and APD90	APD at 30, 50, 70 and 90% of repolarization respectively
ASAT	Aspartate aminotransferase
AUC	Area under the curve (s)
AVB	Atrio-ventricular block
AVN	Atrio-ventricular node
AVNERP	Atrio-ventricular nodal effective refractory period
BCL	Basic cycle length
Bid	Bis in die
BLQ	Below the limit of quantification
CAO	Circumflex coronary artery
CBF	Coronary blood flow
CHO	Chinese Hamster Ovary
CL	Cycle length
C_{max}	Maximum plasma concentration observed
CO	Cardiac output
DAD	Delayed after depolarization
DBP	Diastolic blood pressure
DMSO	Dimethyl sulphoxyde
DT	Developed tension
dV/dt_{max}	Maximum rate of depolarization
EAD	Early after depolarization
ECG	Electrocardiogram
ERP	Effective refractory period
FVF	Fatal ventricular fibrillation
GLP	Good Laboratory Practice
hERG	Human ether-a-go-go related gene
HPLC	High performance liquid chromatography
HPLC-MS/MS	HPLC Tandem Mass Spectrometry
HR	Heart Rate
IC_{50}	Inhibitory concentration decreasing a response by 50 %
Iv	Intravenous route
LOAEL	Low-observed-adverse-effect-level
LOQ	Limit of quantification
LSC	Liquid scintillation counting
LVSP	Left ventricular systolic pressure
MAP	Mean arterial pressure
MAPD	Monophasic action potential duration
MAPD90	MAPD at 90% of depolarization
MTD	Maximum tolerated dose
MVO2	Oxygen consumption
NADPH	Reduced pyridine nucleotide
NaF	Sodium fluoride
NO	Nitric oxide

NOEL	No observed effect level
Od	once daily
PCE	Polychromatic erythrocytes
PEG	Polyethylene glycol
PES	Programmed electrical stimulation
PLA	Plateau amplitude
PMI	Post myocardial infarction
Po	Oral route
PVB	Premature ventricular beat
QRS	Complex duration on the ECG
QT	Ventricular interval duration on the ECG
QTc	Corrected QT
QTcB	QTc according to Bazett
RBC	Red blood cells
RP	Resting potential
SAP	Scientific Advisory Panel
SBP	Systolic blood pressure
SCL	Sinus cycle length
SEM	Standard error of the mean
SOP	Standard operating procedure
SR	Sinus rhythm
T3	3,5,3'-Triiodothyronine
T4	Thyroxine
TdP	Torsade de Pointe
T_{max}	First time to reach C_{max}
TSH	Thyroid stimulating hormone
UDS	Unscheduled DNA synthesis
VERP	Ventricular effective refractory period
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WBC	White blood cells
WCL	Wenckebach cycle length

I. CHMP RECOMMENDATION PRIOR TO THE WITHDRWAL

Based on the review of the data on quality, safety and efficacy, the Rapporteur considers that the application for Multaq, in the treatment of rhythm and rate control in patients with atrial fibrillation or atrial flutter, to maintain normal sinus rhythm or to decrease ventricular rate, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The main concerns of the CHMP were:

- Drug-interaction profile
- No actively controlled studies performed
- Overall safety profile.

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II. EXECUTIVE SUMMARY

II.1 Problem statement

Sanofi-aventis filed a full application for a medical product using the Centralised Procedure containing a new active substance: dronedarone hydrochoride. The intended tradename is Multaq. The CHMP appointed Dr. B. Van Zwieten Boot from the Netherlands as Rapporteur and Dr. Thristrup from Denmark as Co-rapporteur.

The proposed therapeutic indication for dronedarone is:

"Rhythm and rate control in patients with atrial fibrillation or atrial flutter, to maintain normal sinus rhythm or to decrease ventricular rate."

The proposed posology is as follows:

"The recommended starting dose of dronedarone is 400 mg twice daily (800 mg daily) in adult and elderly patients. Treatment with Multaq can be initiated in an outpatient setting. Multaq should be taken as one tablet with or shortly after the morning meal and one tablet with or shortly after the evening meal. Doses higher than 800 mg are not recommended. If a dose is missed, patients should take the next dose at the regularly scheduled time and should not double the dose."

II.2 About the product

Dronedarone (SR33589B) is an anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds that also includes amiodarone. Dronedarone demonstrates electrophysiological characteristics belonging to all 4 Vaughan-Williams classes of anti-arrhythmic compounds:

1. To a limited extent it blocks sodium (I_{Na}) channels decreasing the slope of the depolarization phase (phase 0) of the action potential (Class I effect);
2. It also has limited non-competitive α and β adrenoceptor antagonist properties (Class II effect);
3. Its primary activity is to block the outward potassium currents involved in cardiac;

repolarization at both the atrial and the ventricular levels, thus prolonging action potential duration (APD) and the refractory period (Class III effect);
4. Finally, it reduces on a limited basis L-type and T-type inward calcium currents (Class IV effect).

Atrial fibrillation is the most frequent sustained arrhythmia, affecting 6% of people older than 65 year. The overall incidence rises with each decade; it is estimated that there are 2.2 million AF patients in the United States and several million in Europe Atrial fibrillation is associated with significant morbidity causing symptoms that include palpitations, chest pain, dyspnea and fatigue. Atrial fibrillation may cause tachycardia-induced cardiomyopathy resulting ultimately in heart failure. Atrial fibrillation is also a major cause of embolic complications. It is estimated that AF is associated with a 5-fold increase in the risk of stroke when it is not associated with rheumatic heart disease and a 17-fold increase when it is. Atrial fibrillation is also associated with a 1.5 to 1.9-fold increase in mortality risk beyond that associated with embolic complications.
Treatment strategies for patients with atrial fibrillation include rhythm control and rate control. It is common practice to restore normal sinus rhythm by pharmacological means or by electrical cardioversion to improve symptoms and to decrease the risk of stroke, but in the absence of anti-arrhythmic treatment during the year following conversion the chance of AF recurrence is about 75%. It has been recently suggested that ventricular rate control rather than rhythm control might be an option in the treatment of patients with AF, in particular in case of recurrence.

While regulatory approvals and indications vary, the currently available pharmacological treatments of AF are summarized according to their most common use as follows:

	Rhythm control	**Rate control**
Anti-arrhythmic		
Class Ia	Disopyramide Procainamide Quinidine	-- -- --
Class Ic	Flecainide Propafenone	-- --
Class II	--	betablockers (eg metoprolol, carvedilol)
Pure Class III	Dofetilide Ibutilide	-- --
Class IV	-- --	diltiazem verapamil
Multifactorial	Sotalol Amiodarone	sotalol amiodarone
Digitalis	-- --	digoxin digitoxin

Despite their known association with an increased mortality risk, class I drugs are used quite often for rhythm control. They are, however, generally contraindicated in patients with structural heart disease, including ischemic heart disease, due to the associated increased risk of pro-arrhythmia in patients with LVD, because of the negative inotropic effect, particularly with class Ic agents. Shown to improve survival in many cardiac conditions, pure class II anti-arrhythmics (i.e, beta-blockers) are generally considered poorly effective for rhythm control but more useful for rate control. As for class I drugs, pure class III drugs (e.g, dofetilide) are efficacious for rhythm control but unlike the older products are seldom used. Due to their high pro-arrhythmic potential (i.e, high incidence of *TdP*), pure class III products must be initiated in-hospital, titrated according to renal function and their effects on QTc-interval monitored. The complicated administration scheme probably explains their low utilization. Class IV drugs and digoxin are mainly used for rate control in patients with permanent AF/AFL or in case of AF recurrence in patients treated with one of the other drugs indicated for rhythm control. While effective, calcium antagonists can lead to side effects (e.g, cardiac conduction disturbances and oedema of the lower extremities) that often require discontinuation. Digoxin is effective for rate control but only at rest. It loses its efficacy during exercise and has a rather low

therapeutic index making its utilization difficult in patients with decreased clearance because of renal failure.

Sotalol and amiodarone are both examples of products with multiple class characteristics. Sotalol, a betablocker (class II) with class III properties has been shown to be effective for the maintenance of normal sinus rhythm and was recently approved in some countries for this indication. Due to the pro-arrhythmic effects (*TdP*) documented in clinical trials, in some countries it is recommended that this drug be initiated in hospital. Amiodarone, a product with predominately class III properties but also properties of all 4 classes, used worldwide for the treatment of AF, has recently been shown to be superior to both sotalol and propafenone for the maintenance of sinus rhythm. Pro-arrhythmic effects are rarely observed with amiodarone. Although a subgroup analysis from a recent study in congestive heart failure (CHF) patients suggested that amiodarone might increase mortality in patients with severe New York Heart Association (NYHA) class III CHF, a large meta-analysis of 8 post-MI and 5 CHF trials including 6553 patients suggested the opposite. Nevertheless, amiodarone can lead to extracardiac complications, e.g, dysthyroidism, pulmonary complications, skin complications, and ocular effects, many of which require drug discontinuation and some of which can be severe. Side effects lead to discontinuation of amiodarone in about 8% of patients within 1 year, 18% at 16 months and up to 23% versus 15.4% on placebo according to a recent meta-analysis.

As obvious above, currently available pharmacologic therapies for rhythm control do not have an optimal benefit/risk profile. Consequently, a new agent efficacious for the maintenance of sinus rhythm with a low pro-arrhythmic potential and good extracardiac safety would have added value for the management of patients with AF/AFL. If that same new agent were also effective for rate control it would have the added advantage of being already "on board" should AF/AFL reoccur.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The clinical program to evaluate dronedarone efficacy and safety for maintenance of sinus rhythm included:

- A dose-ranging study: DRI3550/DAFNE: placebo versus 400, 600 and 800 mg BID in patients with AF.
- Two confirmatory studies EFC3153/EURIDIS and EFC4788/ADONIS: both placebo versus 400 mg BID in patients with a prior episode of AF/AFL.

The clinical program to support the ventricular rate control indication included:

- One specific confirmatory study EFC4508/ERATO: placebo versus 400 mg BID in patients with permanent AF.
- Supportive data from DAFNE, EURIDIS and ADONIS in patients with AF/AFL.

Additional studies were performed in populations other than patients with AF/AFL.

- DRI3151 and LTS3841 evaluated the interaction of dronedarone with the functioning of an implantable cardioverter defibrillator (ICD).
- EFC4966/ANDROMEDA evaluated dronedarone's effect on death and hospitalization for heart failure in patients with a recent hospitalization for a severe (NYHA class III or IV) symptomatic episode of CHF and with LVEF ≤35%. Both studies provided additional safety data in patients at high risk of proarrhythmia.
- A study EFC5555/ATHENA evaluating the efficacy of dronedarone 400 mg BID versus placebo for the reduction of cardiovascular hospitalization and death in a population of elderly or high risk patients with AF/AFL started in June 2005.

Clinical trials have been carried out according to general CHMP guidance documents. Relevant for the current indication is the NfG on Antiarrhythmics (CHMP/EWP/237/95). Reference to this document will be made in the clinical assessment. It has been noted that the development plan and application were not in full compliance with this guideline or discussions on development with Competent Authorities.

II.4 General comments on compliance with GMP GLP, GCP

The information submitted in the quality documentation is in accordance with GMP.
The drug product manufacturing site Sanofi Winthrop Industrie, Ambarés, France was inspected by FR competent authority on 8 December 2002 and found to be in compliance with EU GMP.
There is no specific quality issues identified that should be specifically addressed during an inspection of the product-manufacturing site.

Toxicity and toxicokinetic studies were conducted in compliance with GLP regulations. The majority of the non-clinical safety pharmacology studies were performed in the early nineties and were not conducted under GLP. The studies were however performed prior to publication of the ICHS7A guideline and considered of adequate quality.

According to the MAH, all clinical studies were conducted in accordance with the ICH Guideline for Good Clinical Practice (ICH E6, 1996), with local regulatory and ethical requirements, and with the Declaration of Helsinki (version in force at the time of study initiation). Audits and inspections were conducted by the applicant and regulatory authorities.
A risk management plan was submitted at a later stage.

II.5 Type of application and other comments on the submitted dossier

In general, the submitted dossier was of adequate quality.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

In general satisfactory documentation has been provided. No major objections are present.
The drug substance is adequately characterized. The EDMF procedure is used. The residual presence of ten impurities with a structural alert has been discussed. Sensitive methods and low limits are provided to control these impurities.

Drug Product

The development of the product is satisfactorily performed and explained. The excipients are commonly used in medicinal products for oral use. Also the packagings are usual and suitable for the product at issue. The particle size of the active substance is important for the manufacture of the tablets. A specification for particle size has been set.
The substance influences bio-availability, yet an in-vivo / in-vitro correlation has not been found. Therefore a tightening of the dissolution specification is asked for.
The phase 3 clinical studies have been performed with products that, except for tablet punches and the presence of a score line, are identical to the product proposed for marketing.
A wet granulation process is applied. Development studies on the granulation-, compression- and coating process have been done with industrial scale batches and provide sufficient validation evidence.
The release specification and in-process controls guarantee consistent control of the product quality. It seems that the product is stable and that no specific storage condition is required.

III.2 Non clinical aspects

Pharmacology

Dronedarone has been found to possess antiarrhythmic properties in AF and in ventricular arrhythmias in several species, in a wide range of experimental models. Dronedarone is a multi-channel blocker with β anti-adrenergic activities which confers to this new drug all characteristics of all four Vaughan-Williams classes of antiarrhythmics: it blocks sodium channels, shows a noncompetitive anti-adrenergic action (class II drugs), prolongs the cardiac action potential and refractory period (class III drugs) and possesses calcium antagonistic property (class IV drugs). Nevertheless, based on the low affinity constant of dronedarone at adrenergic receptors, the mechanisms underlying these effects remain incompletely understood.

In vitro electrophysiology showed that the rate of rapid ascending phase of AP was decreased in ventricular conducting (Purkinje fibres) and contractile (ventricle) tissues. This effect was due to an inhibition of rapid sodium channel demonstrated in human atrial myocytes. The depression of dV/dt_{max} was frequency-dependent (becomes larger at shorter cycle lengths of stimulation) and was use-dependent with rapid onset and offset of block comparable to those characteristics of class IB agents like lidocaine and amiodarone. The class I property, which would be more pronounced during tachycardia, was relatively modest since, in the several *in vivo* studies carried out, QRS interval was not significantly changed.

In vitro effects on APD with acute *in vitro* exposures of dronedarone, as well as amiodarone, depended on the tissue and the animal species. These differences between each cell types, which had different composition of inward and outward currents, suggested that the AP lengthening effect, due to outward current block by dronedarone (I_{Kr}, I_{Ks}, I_{sus}) counteracted the AP shortening effect due to inward current (mainly L-type Ca^{2+} current) blocked by dronedarone: the outcome was different according to the cell type. The multi-channel blocking properties of dronedarone, namely inhibition of inward and outward currents, produced opposing effects which might explain (i) the homogenization of repolarization, and (ii) the prevention or the reduction of EADs and DADs observed after acute action of dronedarone in the following experiments. *In vitro*, dronedarone diminished the transmural dispersion of repolarization in dogs; principally by shortening the M cell APD and slightly prolonging the APDs of endocardial and epicardial cells. *Ex vivo* or *in vivo*, it eliminated EADs and EAD- or DAD-induced triggered activity elicited by almokalant, dofetilide or strophantidine in canine ventricle and did not change or slightly lengthened QTc in dog and pig hearts. If APD was not always prolonged by dronedarone and amiodarone, and although ERP mainly depended on APD, ERP was always and clearly lengthened in atrium and weakly increased in ventricle. All these effects demonstrated class III antiarrhythmic property.

Dronedarone blocked the L-type calcium current use-dependently and produced a hyperpolarizing shift in the inactivation curve of $I_{Ca\text{-}L}$. These results suggested that dronedarone had affinity for Ca^{2+} channels in the inactivated or depolarized state. Dronedarone thus displayed Ca^{2+} channel antagonist or class IV antiarrhythmic properties like amiodarone. The inhibition of $I_{Ca\text{-}L}$ induced a reduction in calcium transient and therefore decreased shortening of isolated ventricular cells, a potential explanation for the decrease in peak tension of isolated papillary muscles by dronedarone. The calcium antagonistic property of the drug might also explain the slowing down of the atrio-ventricular node conduction in dogs and consequent increases in PQ and AH intervals and prolongation of Wenckebach's cycle length. However the increase in PQ and AH intervals could also be attributed in part to the decrease in HR.

In vivo electrophysiological studies showed that dronedarone had more pronounced effects on atrial and nodal parameters (HR, PR and AH intervals, AERP and AVNERP) and at lower concentrations than on ventricular parameters (HV and QRS intervals, VERP). These observations suggested that dronedarone was more effective at supraventricular than at ventricular levels. Like amiodarone, dronedarone possessed noncompetitive α and β adrenoceptor antagonist properties. Dronedarone showed only weak direct α and β adrenoceptor interactions, but partially blocked isoprenaline-induced tachycardia and adrenaline-induced hypertension. The basis for these anti-adrenergic actions is poorly understood even though calcium antagonist activity after acute and chronic treatments and down regulation in β-adrenoceptor number and reduction in noradrenaline plasma concentration after chronic treatment may be counted. The antagonism of isoprenaline-evoked responses indicated that

dronedarone possessed class II antiarrhythmic properties, and thus the reduction in HR and in AVN conduction velocity described above (AH, PQ intervals and Wenckebach's cycle length increases), might be related to this property in addition to the class IV property. Dronedarone reduced L-type and T-type calcium currents and pacemaker current (I_f) of sino-atrial node (physiological pacemaker); these effects induced diminution of the slope of slow diastolic depolarization (phase 4 of AP) and thus reduction in spontaneous SR of isolated atrium. Dronedarone also reduced the delayed rectifier potassium of pacemaker cells leading to increase in APD and, thus, sinus cycle length. The decrease of SR or HR was observed in isolated atria or hearts in all experiments and in the majority of cases in *in vivo* studies. In some canine models, dronedarone induced an increase in HR (not observed with amiodarone) just after intravenous or oral administrations. As the HR was the result of the decrease in the spontaneous sino-atrial rate, the sympathetic tone (decrease in HR by anti β-adrenergic action) and the vagal tone (increase in HR by $I_{K(Ach)}$ inhibition), predominance of anti-vagal tone was suggested but exploratory studies did not confirm this hypothesis.
The multifactorial mechanisms of action of dronedarone contributed to its hemodynamic effects. Dronedarone had significant α_1-, β_1- and β_2-adrenoceptor blocking effects and calcium antagonist properties that might contribute to the vasodilating and, possibly, to the negative inotropic effects. However, as stated before, the apparent discrepancy between affinity and efficacy was not explained. Also, dronedarone transiently increased coronary blood flow in dogs and showed *in vitro* vasodilatory properties in coronary arteries of the isolated heart; this effect was likely related to the activation of nitric oxide pathway. Main haemodynamic effects of dronedarone were the decrease in contractility (LV dP/dt_{max}) and the increase in LV end diastolic pressure observed at relatively high concentration and mainly after intravenous administration. At higher iv doses, dronedarone exerted a negative inotropic effect, which might be offset by a reduction in after load that also occurred, and cardiac output was maintained or increased in anesthetized dogs or pigs. The left ventricular ejection fraction and fractional shortening (ECG measurements) of PMI (healed) conscious dogs were not modified after chronic oral treatment.
The antiarrhythmic activity of dronedarone has been established in a wide variety of experimental models including auricular and ventricular arrhythmias. Experimental models at ventricular level were more numerous than those in AF models because initially the research of a new amiodarone-like compound, with a better safety profile, was focus on ventricular arrhythmias. In *in vitro* studies, dronedarone, after an *ex vivo* iv treatment, prevented spontaneous AF induced by hypokalemic media (1.4 mM). In AF model induced by electrical burst in the dilated atrium, the drug at 0.1 µM restored 100% of hearts to sinus rhythm. In anesthetized dogs AF was induced by acetylcholine infusion or by vagal stimulation, dronedarone restored sinus rhythm with effective i.v doses about 3 times lower than amiodarone. Like amiodarone, dronedarone with a multifactorial mechanism of action, is effective in several ventricular arrhythmias. After i.v and acute or chronic p.o administrations, dronedarone was a potent antiarrhythmic agent in ischemia- or reperfusion-induced arrhythmias (VF, VT and PVBs) in rats as well as pigs. In canine models, repeated infusion of dronedarone restored sinus in ouabain-induced VT or prevented sudden death (VF) following an ischemic insult developed in a region remote from an infarct; in this model, chronic oral treatment of dronedarone was ineffective. But in other canine model where VF was provoked by a sympathetic hyperactivity with a healed myocardial infarction, chronic oral administration of dronedarone, like amiodarone, prevented VF. This antifibrillatory effect, greater than that observed with a pure anti-adrenergic intervention, was likely to depend upon multiple actions on vulnerable parameters involved in the genesis of lethal arrhythmias of ischemic origin. During pharmacology studies, pro-arrhythmic effects caused by dronedarone were not observed much. In *in vitro* experiments dronedarone had never brought on pro-arrhythmias, on the contrary it suppressed EAD and DAD induced by pure class III antiarrhythmic agent, dofetilide, or by Na-K pump inhibitor, strophantidine in canine Purkinje fibres. In *in vivo* experiments, dronedarone (as well as its metabolite SR35021) induced some case of A-V blocks at 10 mg/kg iv in anesthetized rats and extra-systoles in anesthetized dogs. These effects were not observed with amiodarone. Dronedarone appeared to promote the induction of VT during programmed electrical stimulation after 3 x 3 mg/kg iv in conscious post infarction dogs. In one anesthetized dog treated with 40 mg/kg od, VF was induced during ventricular pacing at day 7. In a model of compensated biventricular hypertrophy by chronic complete A-V block, after chronic oral treatment by dronedarone (20 mg/kg bid), TdP occurred in 4 of 8 animals versus 1 of 6 in vehicle group in anesthetized dogs; whereas amiodarone (40 mg/kg od) did not induce TdP in 7 dogs. This discrepancy between both drugs may be

due to dissimilar electrophysiological and haemodynamic baseline values (before treatment), which were less altered in the amiodarone group than the control and dronedarone groups. In this experiment, plasma levels (1.3 µg/mL) of dronedarone were clearly higher than that usually observed in dog and man (0.08 to 0,15 µg/mL), whereas plasma levels of amiodarone (3.5 µg/mL) were slightly greater than that measured in patients (1.5 to 2.5 µg/mL). Most of these arrhythmic effects have been obtained with the highest intravenous doses or at high plasma concentrations and tissue level after chronic oral treatment.
The pharmacology studies have shown that dronedarone was 3 to 20 times more potent than amiodarone in *in vitro* experiments; haemodynamic, electrophysiological and antiarrhythmic effective doses of dronedarone were about 3 times lower than those of amiodarone after acute iv and po administration in rats, dogs or pigs. But after chronic oral treatment, effective doses of dronedarone were similar or upper to those of amiodarone; measurements of plasma and cardiac tissue concentration showed that dronedarone and SR35021 values were clearly inferior to those of amiodarone and deethylamiodarone (metabolite of amiodarone), respectively. Thus, dronedarone was intrinsically a more potent antiarrhythmic agent with a higher metabolic clearance and less accumulation than amiodarone.
Two metabolites have been studied. SR35021A displayed antiarrhythmic, electrophysiological and haemodynamic activities similar to those of dronedarone but was less potent (approximately 3 to 10 times) than its parent compound. SR90154 has very little or no activity. Plasma levels of SR35021A were about 10 times lower than those of dronedarone.

Safety pharmacology studies showed the following. In mice, the only observed effect on the central nervous system was a decrease in spontaneous activity from the dose of 200 mg/kg and above after oral administration. In anesthetized dog, administered by the intraduodenal route, dronedarone induced at 12.5 and 25 mg/kg a dose-dependent decrease in mean arterial blood pressure associated with a vasodilator effect, an increase in stroke volume and cardiac output associated with a decrease in total peripheral resistances. No ECG changes were observed.
In anaesthetized dogs an increase in respiratory rate was noted. In the guinea pig, dronedarone administered orally did not affect respiratory function up to and including the dose of 100 mg/kg.
On the gastrointestinal tract, dronedarone in mice and rats had no effects up to the dose of 100 mg/kg.
On the hydroelectrolytic balance, the only observed effects in the rat were a decrease in endogenous creatinine clearance (from 30 mg/kg in females and at 100 mg/kg in males), a decrease in urinary volume associated with slight changes in excreted quantities of electrolytes (100 mg/kg only in both sexes). Repeated dronedarone administration (up to 30 mg/kg orally in male rats) over 2 weeks was devoid of effects on renal blood flow, urine production and creatinine clearance.
After 14-day repeated administration, dronedarone unlike amiodarone induced no phospholipid accumulation in lung (up to 150 mg/kg) and phospholipid accumulation in liver at 100 mg/kg only. 150 mg/kg produced a slight and non dose-dependent increase in liver phospholipids.
In contrast to amiodarone, no major modification on thyroid hormone levels was noted with dronedarone (decrease in T4 (T4/T3 ratio)). No effect on behaviour of mice was observed up to and including the dose of 10 mg/kg iv. A slight and transient decrease in body temperature was observed after dronedarone 30 mg/kg iv. No effects on muscle tone and motor coordination and spontaneous motor activity were observed.
The following cardiovascular effects were observed after intravenous dronedarone administration: decrease in arterial blood pressure and left ventricular pressure, a negative chronotropic effect and moderate increases in stroke volume and cardiac output associated with a decrease in total peripheral resistances. PR interval was increased for approximately 60-90 min at the dose of 5 mg/kg whereas other ECG time intervals were unchanged. No abnormalities in renal function were observed after intravenous administration of dronedarone at 1 and 3 mg/kg.

Pharmacokinetics

The ADME studies described in mice, rats, rabbits, dogs and macaques provide a view of the disposition of dronedarone and its active metabolite in animal species. Single- and repeat-dose studies have been conducted at dose levels within the range of dosages tested for the safety evaluation program.

Data indicates that oral doses of dronedarone were well absorbed. The time of maximum plasma concentration after oral administration is between 1 to 4 hours whatever the species. Once absorbed, dronedarone undergoes an extensive first pass extraction resulting in low absolute oral bioavailability in the species tested.
The apparent terminal half-life values of dronedarone after oral administration were between 2 and 7 hours in mice, rats and dogs. However, these data are questionable. According to the assessor, elimination half life in rat and dog is probably longer because in repeated dose studies accumulation of dronedarone is observed.
In all animal species the exposure increased more than dose proportional and some drug accumulation was observed (up to 4-5 fold increase in AUC in dogs as compared to single dose studies).
Dronedarone and its active metabolite are both highly bound to plasma proteins in all species including human and not saturable up to 10000 ng/mL. In human plasma it appeared to be difficult to assess the fraction unbound. In a study using equilibrium analysis plasma binding was 99.84 – 100%, whereas a study using ultrafiltration pointed at a binding percentage of 99.14%. Dronedarone does not distribute extensively into red blood cells.
The pharmacokinetics of dronedarone following intravenous administration in rats and dogs are characterized by a large volume of distribution (around 12 and 39-66 L/kg in dogs and rats, respectively) and a high clearance (about 2-4 L/h/kg).
Dronedarone is widely distributed in tissues. The tissues with the greatest radioactive levels are liver > kidney = lung = adrenals = pancreas = spleen = pituitary gland > thyroid = salivary glands = brown fat > Harder's glands = pineal body > heart. In pigmented animals, additional specific binding to melanin-containing structures, such as skin and eyes, was also observed. Dronedarone and/or its metabolites crosses the blood-brain barrier, the placenta and is excreted into milk.
Dronedarone undergoes extensive metabolism. The main metabolites of dronedarone observed in humans are also observed in the animal species tested.
Dronedarone is an inducer of CYP3A in mice and exhibits no biologically significant inducing effect on CYP-dependent reactions in rats and dogs. This effect seems to be limited to mice since it was not observed in rats, dogs and humans.
Dronedarone is rapidly eliminated by metabolic clearance with no excretion of unchanged dronedarone in bile (rat) and in urine (mice, rat, dog, macaque). The major route of excretion of the total radioactivity is the feces via the bile with less than 9% of the dose in urine.

Toxicology

Consistent with the pharmacological properties of the compound, electrocardiographic changes were noted from the lowest tested oral dose in rats (2 mg/kg/day; i.e. at non-detectable exposure levels) and from 25 mg/kg/day in dogs (i.e. at 5-8 human anticipated clinical exposure).
Slight effects on the gastrointestinal tract were noted both in dogs and rats. In rats, the exposure based safety margin for these effects was only 2. In dogs however, these effects occurred at exposures with sufficient safety margin (20 and higher) compared to clinically anticipated exposures.
In rats, there was no clear correlation between transaminase elevations and the occurrence of minimal foci of liver necrosis. As a result of dose reduction the macro- and microscopic gastrointestinal changes observed in the 2-week studies in rats (i.e. liver) and dogs (i.e. biliary system) were not confirmed in the longer term studies in these species. As these effects occurred at exposures well beyond the clinical anticipated levels, they were not relevant. Phospholipidosis, as evidenced by foamy macrophages in several tissues, is an important unwanted effect of amiodarone. The applicant modified the molecule of dronedarone such that phospholipidosis was unlikely to occur. Compared to amiodarone, dronedarone is less lipophilic, has a higher metabolic clearance and a shorter half life. All these characteristics might lead to lower tissue accumulation of dronedarone. A comparative safety pharmacology study pointed to the lower potential of dronedarone to induce phospholipidosis. In the 3 month rat study foamy macrophages were observed in the lungs and lymph nodes of rats. The effects in the lymph nodes occurred at an exposure levels without an exposure based safety margin. Phospholipidosis was not aggravated after a longer treatment (6 months) employing similar dose levels in rats. In this study a (reversible) increase in perivascular lymphoid hyperplasia was observed. In the rat carcinogenicity study, macrophage infiltration was observed in lungs, and to a lesser extent in mesenteric lymph nodes, at the high dose only (3-6 times clinical exposure levels). Macrophage

infiltration of mesenteric lymph nodes occurred in dogs only at supra therapeutic exposure levels (> 20 times human exposure). In the studies conducted by the intravenous route in both rats and dogs, although the exposure was much higher compared to the oral route no macrophage infiltration was noted.
As described in the safety pharmacology section, a comparative study on the effects of dronedarone and amiodarone on the thyroid showed that dronedarone only slightly modified circulating thyroid hormone level, whereas with amiodarone, rT3 was increased (2- to 4-fold) and so was T4/T3 (14 to 29%).
Hormone levels were investigated during the chronic studies in rats and dogs. Changes observed with dronedarone were minor and differ from those induced by amiodarone: decrease in T3 mainly (i.e. -15 to - 25% in rats at 1-2 times human exposure levels, and -15 to -50% at 1-2 times human exposure levels in dogs), without any change in TSH, and in the rat only increased incidence of high follicular epithelium. The modifications caused by amiodarone were marked (historical comparison): T4 increased 1.5- to 4- fold and TSH increased 2- to 3-fold in rats, T4 increased 2- to 4- fold in dogs and histological changes consistent with increased thyroid activity were observed at microscopic examination, carcinogenicity studies included adenoma and adenocarcinoma in the latter. No changes in the thyroid were observed in the carcinogenicity studies conducted with dronedarone.
Slight renal functional alterations were noted in the toxicity studies and appeared as minor plasma and/or urinary biochemistry changes. There were no microscopic changes in the kidney in any of the studies. Nevertheless, effects on plasma creatinine occurred at ≥ 0.5 times the human exposure levels in the 3-month and 6-month chronic studies. A dose effect relationship could not be established. No creatinine increase was observed in dogs. Protein was detected in the urine of macaques. The effects on creatinine were mentioned in this summary due to the systematic increase in the creatinine plasma levels observed during clinical development both in healthy volunteers and in patients. An effect of the compound on renal function cannot be excluded. A battery of genotoxic studies were done. All tests were negative and only the HPRT test yielded equivocal results. Two other in vitro genotoxicity assays were negative.
In the carcinogenicity studies, dronedarone produced a treatment-related increase in mortality in male mice and resulted in an increase in proliferative changes in the haemolymphoreticular system in male and female mice (histiocytic sarcoma), in mammary glands in female mice (adenocarcinoma) and in the mesenteric lymph nodes in both species (angiomatous hyperplasia and hemangioma in both species, hemangiosarcoma in female mice only). All these effects occurred at the highest dose tested leading to exposure level which is 10 fold the clinically anticipated levels. In repeat dose and carcinogenicity studies dark discolouration of mesenteric lymph nodes was observed being the result of blood stasis. Clinical relevance of these effects is unknown.

In the fertility and early embryonic development studies, Dronedarone was without adverse effect in rats on oestrus cycles, mating performance and fertility. During embryo-fetal development studies performed in rats, dronedarone was found to be teratogenic in the rat at 100 mg/kg/day.
Dronedarone was slightly phototoxic in guinea pigs at high dose levels.
With respect to the environmental risk assessment, the action limits have been exceeded and therefore a phase II assessment needs to be completed.

III.3 Clinical aspects

III.3.1 Pharmacokinetics

In total, 7 bioequivalence/bioavailability, 40 clinical pharmacology, six efficacy/safety and 10 in vitro studies were performed in patients and healthy volunteers to elucidate dronedarone's pharmaceutical, pharmacological and clinical characteristics.

Drug formulation

An extensive drug development programme was targeted towards ameliorating the strong impact of concomitant food intake on oral bioavailability of the lipophilic compound dronedarone: an up to 27-fold increase in extent of exposure was observed. After adding a surfactant the final developed

formulation displayed fed versus fasted ratios of 2.3 to 4.6 for dronedarone and 2.2 to 3.7 ratios for the main metabolite (SR35021). The pivotal bioequivalence study with the improved tablet formulations demonstrated the similarity of tablets used in the most important clinical studies. The type of meal seems not relevant for dronedarone bioavailability of the optimised tablet formulations with the surfactant when compared with the 2- to 4-fold impact any food-intake has as compared to intake under fasted conditions. A high-fat meal led to a 30% increase in dronedarone and SR35021 exposure compared to a low-fat meal, this may still be cause for concern also in view of the observed interindividual variability. Although no food-interaction study was performed with the to-be-marketed formulations it is obvious that food will influence dronedarone pharmacokinetics. Therefore, dronedarone was recommended to be taken with/after a meal in the clinical efficacy/safety studies and consequently in the SPC recommendations. In the majority of clinical pharmacology studies dronedarone was administered with food and the tablets used in the clinical trials were similar to the to-be-marketed tablets. The tablet to-be-marketed 2E5 differs only in engraving to tablet 2E3, a bioequivalence study with this tablet is not needed.

Absorption

Dronedarone is well-absorbed after oral administration (70 to 94%) in fed conditions. Absolute bioavailability due to presystemic first pass metabolism is under fed conditions only 15%. As mentioned food increases dronedarone's absorption.

Distribution

Dronedarone and its main metabolite SR35021 exhibit high levels of in vitro plasma protein binding (>98%), mainly to albumin. Binding to α1-acid glycoprotein (AAG) under normal conditions has no relevance but may gain importance when AAG concentrations are increased, such as during infectious diseases. After IV administration a large volume of distribution (Vss) ranging from 1200-1400 L is observed. The ratio of red blood cells/plasma dronedarone concentrations was approximately 1. Dronedarone has been shown in animal studies to cross the blood brain barrier and the placenta and is excreted into breast milk.

Metabolism

Dronedarone is extensively metabolised mainly (>84%) by CYP3A4. A higher proportion of metabolites are found after oral than after IV administration indicating a relevant first pass effect. Although there is some evidence that CYP3A4 allelic distribution may differ among populations, there is limited evidence that the resulting protein variants have a substantial effect on enzyme function in vivo. Problems with polymorphism for dronedarone metabolism are therefore unlikely.
Dronedarone itself did not appear to be a substrate for CYP2D6, but was shown to inhibit CYP3A4 and CYP2D6. Dronedarone did not induce CYP1A1, CYP1A2, CYP2A and CYP3A nor inhibit CYP1A2, CYP2C9, CYP2C19 and CYP2E1 isoenzymes. The main metabolite SR35021 was shown to inhibit in vitro all CYP isoenzymes tested (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4). The clinical development program of Multaq has therefore been set up to address potential interactions with CYP3A4, CYP2D6, CYP2C9 and CYP1A2 isoenzymes. The influence of CYP2C8 or CYP2B6 on dronedarone metabolism was not yet been investigated.
The N-debutyl metabolite SR35021 exhibits pharmacodynamic activity but is 3 to 10-times less potent than dronedarone. After oral administration similar plasma levels of SR35021 compared to dronedarone are observed. SR35021 is however somewhat less extensively bound to plasma protein, dronedarone 99.74 ±0.03%, SR35021 98.21±0.4%. Therefore, based on the similar or slightly lower total exposure of SR35021, the 3.5-fold higher unbound exposure and the 3 to 10 times lower activity as compared to dronedarone, SR35021 is expected to contribute to the pharmacological effect of dronedarone.

Excretion

Following oral administration 84% and 6% of the dronedarone dose is excreted mainly as metabolites in feces and urine respectively. After iv administration the plasma clearance of dronedarone ranges from 130 to 150 L/h and is independent of the dose. Plasma elimination has a bi-phasic profile and steady state terminal half-lifes ($t_{1/2z}$) of dronedarone ranges from 27 to 31 h and that of SR35021 ranges from 20 to 24 h. After a 14-day washout period dronedarone and its metabolite are not detectable in plasma anymore. Due to the biphasic elimination profile the second phase of the concentration time curve does not contribute much to the total extent of dronedarone extent of exposure. Therefore, despite 30 hours $t_{½z}$ plasma concentration time profiles seem more constant after 400 mg BID instead of 800 mg OD dronedarone administration. Thus, from a pharmacokinetic point of view a twice daily dosing regimen seems defendable. This is supported by the pharmacodynamic data (see section II.2).

Dose-linearity and multiple dosing

Dronedarone exposure increases supra proportional. After a two-fold dose increase plasma levels of dronedarone and its main metabolite increase 2.4- to 3-fold. Steady state at the clinically relevant dose of 400 mg BID is reached after 4 - 8 days. Based on C_{trough} values in the higher dose range > 800 mg BID it may take longer before steady state is reached than in the therapeutic dose range. An accumulation rate of 2.6 to 4.5 seems independent of the dose in the range of 200 mg to 800 mg dronedarone administered BID. A larger than expected accumulation rate based on single dose data was observed probably due to a saturated first pass metabolism. Accumulation rates at higher than therapeutic doses are somewhat larger in the range of 3 to 7. After repeated dosing of 400 mg dronedarone BID in fed conditions, mean $C_{max,ss}$ ranges from 84 to 167 ng/mL for dronedarone and from 66 to 119 ng/mL for SR35021. The extent of exposure (AUC_{0-12}) ranges from 650 – 1030 eng*h/mL for dronedarone and from 534 – 930 ng*h/mL for SR35021.

Under fasted conditions intra-individual PK variability of dronedarone pharmacokinetics is considerable (C_{max} ~34%; AUC ~18%), but under fed conditions intra-individual PK variability is moderate (C_{max} 18 – 26%; AUC_{0-12} 10 – 18%) and similar in a patient and healthy volunteer population. Intra-individual variability is estimated from residual coefficients of variance as no replicate-design studies were performed. Interindividual variability is in the range of 30% to 37% under fed conditions. Dronedarone can be considered as a drug with only a limited PK variability under, clinically relevant, fed conditions.

Target population

Combined sparse sampling data from EURIDIS/ADONIS/ANDROMEDA/ERATO/DAFNE clinical trials indicate that dronedarone's pharmacokinetic characteristics in patients, i.c. C_{trough} and C_{max} , are comparable to those in healthy volunteers.

Special patient populations
A limited clinical pharmacology program in special populations was performed with dronedarone.

Hepatic impairment
The anticipated clinically relevant impact of hepatic impairment was not yet elucidated.

Renal impairment
The lack of a study in patients with renal impairment is acceptable as dronedarone undergoes limited renal excretion only, approximately 6%. The lack of significant effect of renal impairment on dronedarone pharmacokinetics is supported by population pharmacokinetics analyses.

Other special populations
In elderly (>65 years) men dronedarone rate and extent of exposure are increased by approximately 23% to 33% when compared to young men. Therefore, age by itself does not have a clinically relevant

impact on dronedarone pharmacokinetics. However, a 1.5-fold increase in exposure was observed in elderly female compared to elderly male. Body weight may explain part of these observed differences. This impact of weight is not investigated in a separate clinical pharmacology study but addressed in the population PK assessment only. Elderly women may therefore have a clinically relevant increase in exposure as compared to younger male patients. A single study was performed in Japanese subjects, which did not point to important differences in pharmacokinetics characteristics as compared with Caucausian subjects. In the clinical efficacy/safety trials only a very limited number of non Caucausian subjects (~1% of total trial population) were investigated. No clinical pharmacology studies were performed in children. This is considered acceptable in view of the proposed indication of AF/AFL, which is uncommon in children.

Population pharmacokinetics
Although clearance was statistically related to age, gender and weight, the clinical relevance of this finding is less clear.

Interactions
In vitro dronedarone is for >84% metabolised through cytochrome P450 3A4 (CYP3A4) isoenzymes and is shown to be itself a moderate inhibitor of CYP3A4 and CYP2D6 isoenzymes. In addition, the main metabolite SR35021 demonstrated a potential for inhibition of CYP2C9, CYP2C19 and CYP1A2 as well.

Co-administered drugs affecting dronedarone exposure
CYP3A4 inhibitors
Potent CYP3A4 inhibitor ketoconazole (200mg OD) increase dronedarone exposure up to 25-fold. Consequently, potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, nefazodone, ritonavir, erythromycin, and clarithromycin are contraindicated in the SPC. Moderate CYP3A4 inhibitors such as calcium-antagonists with heart-rate lowering effects, verapamil (240 mg OD) and diltiazem (240 mg OD) increase dronedarone exposure 1.5-fold and 1.7-fold respectively. A low verapamil dose was evaluated and a more pronounced effect on dronedarone exposure with higher verapamil doses in clinical practice is likely. In view of an observed impact on pharmacodynamics (QTc and PR increases) with verapamil, co-administration of verapamil and diltiazem cannot be recommended because of potentiation of negative chronotropic properties and slowing of conduction. Initial lower dronedarone doses or downward dose adjustments of dronedarone when co-administered with moderate CYP3A4 inhibitors in general or with the heart-rate lowering calcium-antagonists in specific should be considered. Co-administration of large amounts (300 ml TID for 10 days) of double-strength grapefruit juice led to a 3-fold increase in dronedarone exposure.
CYP3A4 inducers
The potent CYP3A4 inducer rifampicin (600 mg OD) leads to a 5-fold lower, clinically ineffective, dronedarone exposure.
CYP3A4 inhibitors and inducers on SR35021 exposure
The impact of CYP3A4 inhibitors and inducers on the active SR35021 metabolite is modest, because of the involvement of CYP3A4 both in its formation and further metabolism. Considering that SR35021 is 3- to 10-fold less pharmacologically potent than dronedarone with similar plasma concentrations under normal conditions, CYP3A4 mediated drug-drug interactions are not likely to influence dronedarone's clinical efficacy and safety through changes in SR35021 exposure.

Absorption modifaction of dronedarone
Pantoprazole did increase dronedarone C_{max} by 13%. Therefore alteration of pH does not influence dronedarone biovailability to a relevant extent. Food increases dronedarone bioavailability 2- to 4.5-fold (see section II.1.3). Meals with a high fat content increase dronedarone exposure 1.2- to 1.5-fold compared to meals with a low fat content. In view of this relatively small impact of the type of meal, dronedarone can be recommended to be taken with food as was done in the clinical efficacy/safety studies without making specific and unrealistic recommendations regarding type of food-intake.

Dronedarone affecting exposure of co-administered drugs

CYP3A4 substrates
Co-administration of dronedarone 400 mg BID to CYP3A4 substrates leads to 2- to 4-fold increases of simvastatin acid and simvastatin levels respectively but has a less pronounced impact on extent of plasma exposure of verapamil (1.3-fold), nisoldipine (1.5-fold) and combined oral contraceptives (levonorgestrel 1.2-fold and ethinylestradiol 1.3-fold). The impact on statins may be clinically relevant, mediated through CYP3A4 and PgP, and could lead to increased risk of statin dose-related adverse events, especially myopathy. The implications of the observed two-way drug-drug pharmacokinetics and pharmacodynamics interaction with verapamil should be discussed by the applicant as suggested above. This interaction profile is even further complicated by both drugs p-gp inhibitory potential. Dronedarone does not have a clinically relevant impact on nisoldipine (in addition no pharmacodynamic interaction was observed) and on oral contraceptive plasma exposure.
P-glycoprotein substrates
Digoxin (P-gp substrate) exposure is increased by 1.7- to 2.5-fold for C_{max} and AUC_{0-24}, respectively, when co-administered with dronedarone 400mg BID. Therefore, when digoxin is co-administered the digoxin dose should be halved and in addition patients should be monitored for clinical, biological and ECG signs of digoxin intolerance.
CYP2D6 substrates
The clinically relevant co-administration of betablockers is influenced by the potential of dronedarone to inhibit CYP2D6. Dronedarone 400 mg BID increased metoprolol steady state by approximately 1.6-fold. A more modest 1.3-fold impact was observed on propranol exposure. Due to the potential for both pharmacokinetic and pharmacodynamic interactions a warning of cautious concomitant use of beta-blockers is warranted.
CYP2C9 substrates
Dronedarone did not demonstrate relevant CYP2C9 inhibition properties in vivo. Losartan (CYP2C9 substrate) C_{max} was 18% decreased and of the major active losartan metabolite AUC was 21% and C_{max} 25% decreased. Warfarin, a CYP2C9 substrate, showed a limited nonclinically relevant potential for interaction with dronedarone: S-warfarin exposure and INR were 1.2- and 1.1-fold increased. The in vivo potential of dronedarone to inhibit CYP1A2 and CYP2C19 is not elucidated yet.

In conclusion, the applicant has not been able to substantiate its claim of having developed a compound with a clinically relevant improved pharmacokinetic profile over the parent compound amiodarone ($t_{1/2z}$ 50 (20-100) days, Vd ~ 70 l/kg). Dronedarone's main pharmacokinetic advantage is that compared to amiodarone its half-life is greatly reduced due to a much smaller distribution volume. These PK characteristics may reduce the long-term pulmonary adverse events observed with amiodarone. It is however the interaction profile of dronedarone that is cause for concern by its inhibition potential of CYP3A4, CYP2D6 and PgP. This inhibition potential makes the relevant co-administration of cardiovascular drugs e.g. beta-blockers, verapamil, diltiazem and specifically digoxin in patients with AF/AFL to a challenge for clinical practice. The absence of dosing alternatives to the investigated 400 mg BID in patients with a risk of increased exposure reduces the clinical potential of dronedarone.

III.3.2 Pharmacodynamics

Dronedarone's pharmacodynamics has been studied using ECG changes of PR and QTc as surrogate markers, while no invasive electrophysiological studies were performed in man. The channel blocking effects are based on in vitro and animal models. Dronedarone decreases HR at higher than therapeutic doses and to a larger extent during exercise testing. At the clinically significant 400 mg BID dose dronedarone showed only moderate changes in SBP and DBP. PR interval was increased as was QTc (10-20 ms with 400 mg BID dose), the latter increasing with dose. The dose range tested indicates that lower than 400 mg BID doses may not be clinically effective, possibly if a 300 mg BID dose had been administered in stead of 600 mg OD this dose might have shown clinical benefit. However, from these PD data the dose range chosen in DAFNE seems defendable, though with hindsight not very fortunate, as a lower daily dose may have had clinical relevance in special patient groups (elderly & female). Dronedarone's antiarrhythmic properties were confirmed in a patient population especially for its heart rate lowering effect with only a limited impact on clinical endpoints; conversion to sinus rhythm (bad) or impact on six minute walking distance test (good). A not very strong PK/PD correlation was

observed for QTc and lower than average plasma ranges may have clinical significances for time to recurrence of AF/AFL, but this finding was not very strong.
Verapamil shows clinical relevant PK and PD interactions (PK/PD other concern), a more limited and predictable impact of co-administered beta-blockers was observed, this is sufficiently addressed in the SPC. No clinically relevant impact is observed on INR and PK characteristics of co-administered warfarin. The possible pharmacodynamic interaction and the fact that only a single warfarin dose has been studied. Since warfarin is not the most commonly prescribed oral anticoagulant in Europe, other OACs may need to be investigated.
The impact of dronedarone on renal function is well investigated by the applicant who makes it plausible that not renal function is influenced but specifically tubular secretion of creatinine is inhibited. However, this may have an impact on organic cationic drugs that undergo tubular secretion. Some increased serum urea levels were reported as adverse events and may indicate some level of renal toxicity. In addition, the implication of losing such an important clinical marker of renal function may have far-stretching impact on daily clinical practice, as was postulated to have happened in the ANDROMEDA trial where ACE-inhibitors and ARBs were mistakenly discontinued because of increased serum creatinine findings.

III.3.3 Clinical efficacy

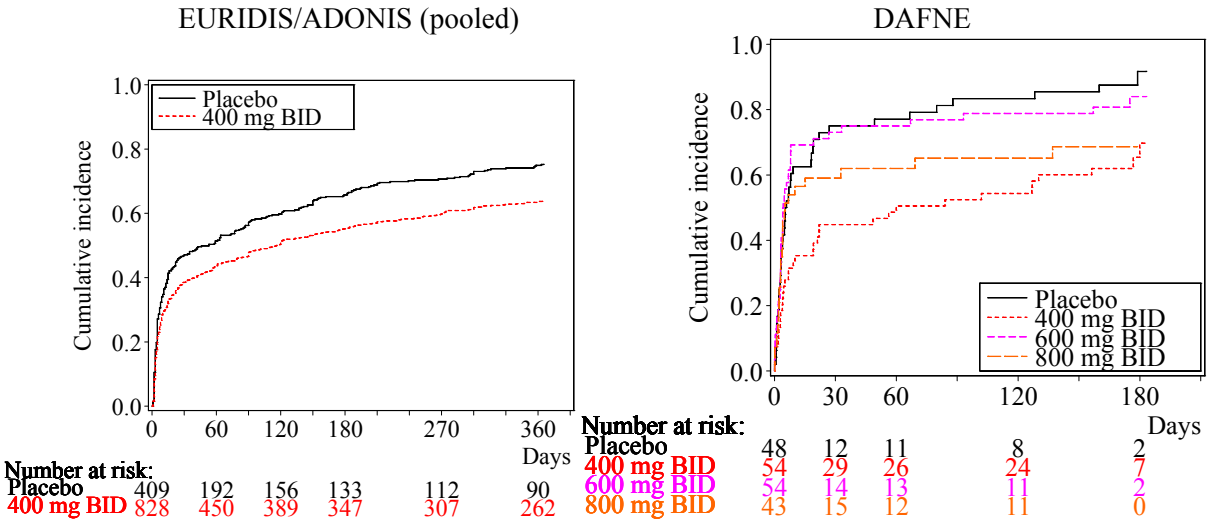
Four main clinical studies were submitted to document the efficacy of dronedarone in patients with atrial fibrillation (AF) or atrial flutter (AFL) for rhythm and rate control. One dose-response study (DAFNE) has been performed, as basis for the main clinical studies intended to study the effects of dronedarone both for rhythm (EURIDIS/ADONIS) and rate (ERATO) control. All studies shared the features of being multinational, multicenter, double-blind, placebo-controlled and of parallel design. They were conducted in accordance with current good clinical practice (GCP) standards and regulatory guidelines. No major differences in demographics were noted, elderly and female patients were adequately represented with almost 50% of the patients older than 65 years and 30% female. Black and Asian patients were underrepresented. Underlying disease included sufficient percentages of patients with structural heart disease, ischemic heart disease, CHF (NYHA class III/IV was contraindicated), valvular dysfunction and arterial hypertension. Concomitant medication that is known to affect heart rate (beta-blockers, digoxin, calcium antagonists) was given in the majority of patients, which is in accordance with daily practice. Some descriptive information was unclear or not well represented, where appropriate specific issues that should be elucidated are raised as concern. Class I and III antiarrhythmics were contraindicated. Randomization and blinding procedures were acceptable, statistical plans adequate.

Dosage regimen (DAFNE study)
The selected dose range was chosen on the basis of ECG effects in the phase 1 studies and varied between 400 mg BID and 800 mg BID. Patients with persistent AF were included for whom cardioversion and antiarrhythmic treatment was warranted with the objective to determine the most effective dose of dronedarone for the maintenance of sinus rhythm in patients undergoing cardioversion for AF. Following an amendment in the protocol, the primary endpoint focussed on time to first recurrence after successful conversion to normal sinus rhythm. This endpoint estimates the proportion of patients with an event (recurrence of AF/AFL in this case) while minimizing bias due to censorship and allows robust statistical analysis using the Kaplan-Meier estimate and the log rank test. The efficacy results did indicate that dronedarone 400 mg BID had a significant effect on maintenance of sinus rhythm after conversion of atrial fibrillation. A difference of median time to AF recurrence of 60 days in the dronedarone 400 mg BID group, compared to 5 days in the placebo group, and a recurrence rate after 6 months of 65% vs. 90%, respectively, was considered clinically relevant. This was further supported by outcomes of the secondary endpoints. Notwithstanding the efficacy of the 400 mg BID dose, this study did raise the issue of dose response. No dose response was seen, in fact when the primary endpoint is taken into account, no significant effects were seen in the median time to first AF recurrence in the PPM population following the 600 mg BID and 800 mg BID dosages. When the Kaplan-Meier curves are taken into account, the 800 mg BID shows some effect, but the 600 mg BID almost nears the placebo group. This difference could be due to the heterogeneity of the groups, but the results contrasted with the effect on non-electrical cardioversion and ventricular rates in case of

recurrence. This needs to be clarified. The lack of dose response again raises the question whether lower dosages would have been effective as well. In view of these findings the absence of dosing alternatives to the proposed 400 mg BID for the sought indication reduces the clinical potential of dronedarone. Unfortunately, as dose dependent ECG effects may play a role in its safety (see below), this has not been studied.

Main clinical studies in rhythm control (EURIDIS/ADONIS)
Due to the similarities in the study design in both studies, these two studies - which were carried out in different parts of the world - were pooled together. This was considered acceptable. The main difference compared to DAFNE was that in this study only patients were recruited who were already in sinus rhythm. Primary endpoint was in accordance with DAFNE study. It is noted that this primary end point, time to the first recurrence of the arrhythmia, is defined as recurrence of atrial fibrillation lasting at least 10 minutes, which is different from the european society of cardiology definition of such a recurrence that is 30 seconds. No major differences were noted between the EURIDIS and ADONIS studies and pooling of the data is considered justified. The cardiovascular histories of the randomized and treated patients were similar in the two treatment groups, except for a higher percentage of patients with hypertension and coronary heart disease in the pooled dronedarone group as compared with the pooled placebo group. It is unlikely that this will have significantly affected the results. Despite these differences, the groups appear well comparable and representative of the population to be treated according to the indication.
The results confirm the data of the dose-response study and show that dronedarone does have a significant effect on the time from randomization to adjudicated first AF/AFL recurrence. Further evidence is obtained by the effect on the secondary endpoints. In absolute terms median time to recurrence is approximately 50 days longer in both groups compared to the DAFNE study which can be attributed to the fact that these patients have already achieved sinus rhythm at the beginning of the study. The majority of the AF/AFL recurrences occurred early following randomization. This could be related to the electrical instability that follows recent AF/AFL episodes. A median difference of 63 days time from randomization to adjudicated first AF/AFL recurrence within 12 months raises the question of clinical relevance. The difference in recurrence rate after 12 months of approximately 10% is smaller than seen in the DAFNE study. A reduction in time to death and hospitalisation was noted but this reflects an ancillary analysis and needs further confirmation, in particular in the context of the negative effects seen in the ANDROMEDA (see below). Relative risks according to selected baseline characteristics and medications for the time to adjudicated first AF/AFL recurrence demonstrated a better treatment effect than placebo for most covariates examined. Similar to the DAFNE study, the effect of dronedarone was less when beta-blocking agents were given. This also was seen when calcium antagonists were given. This needs further clarification.

Figure 1 Time to adjudicated first AF/AFL recurrence



In summary, the pooled data of the EURIDIS and ADONIS do show a significant effect in terms of rhytm control in patients with atrial fibrillation and possibly atrial flutter, but the clinical relevance needs further consideration. In this regard, the absence of actively controlled studies is considered a major lack in the dossier. In the NfG on antiarrythmics (CPMP/EWP/237/95) it is stated explicitly that it should be necessary to compare the investigational compound under randomised, double-blind conditions with one or more established drugs of various types in order to define its place in therapy. Dronedarone has been developed as an alternative for amiodarone, so it would be logical to require a comparative study with this compound, but comparison with sotalol could also be considered. In the clinical overview the MAH states that head-to-head comparisons are frequently not possible (ie, conditions of use too different such as for dronedarone) or if possible of low quality (ie, open-label, etc). Instead, a weak attempt is made to correlate through historical placebo, but it is concluded that efficacy for AF/AFL prevention varies considerably across studies. However, well-designed comparative studies are being performed, such as the SAFE-T (comparing amiodarone versus sotalol, ref. NEJM 2005; 352: 1861), allowing a better assessment of the benefit/risk ratio. The lack of such a study is considered a major objection against registration for the indication of rhythm control.

Main clinical study in rate control (ERATO).
The patient population recruited for this study included permanent AF patients defined as having AF for more than 6 months. No patients with AFL were recruited, although the proposed indication includes those patients as well. The implication is that these patients cannot be included for this part of the indication. The same dose of 400 mg BID was chosen for this study based on the results of the dose finding study DAFNE because it was proven to be effective in comparison to placebo for controlling heart rate during the first recurrence of AF. This was confirmed in the EURIDIS/ADONIS studies. In the DAFNE study dose-dependency was observed, but, as ECG effects, in particular effects on QTc, may be enhanced at higher dosages, this is considered justified.
Regarding the inclusion and exclusion criteria, they differ from those of previous studies in the sense that they did not mention exclusion of patients whom previously showed treatment failure under other anti-arrhythmic drugs. The primary efficacy variable was the change in mean HR measured by a 24-hour Holter recording at rest on Day 14 (steady state) compared to baseline. Duration of the study is limited to 4 months, but this is considered sufficient to assess maintenance of effect on heart rate. Data confirm that dronedarone can reduce heart rate in patients with chronic AF when measured after 14 days of treatment during both Holter monitoring (diurnal and nocturnal) and exercise testing.
Reduction in heart rate ranges between 10 – 12 bpm, at rest up to 31 bpm at maximal, compared to placebo. Holter monitoring after 4 months showed maintenance of the effect without interaction with other heart-rate lowering agents (beta blockers, calcium antagonists and digitalis). These changes in heart rate lowering effect were neither accompanied by improvement in exercise testing, nor by improvement in gas exchange parameters and anaerobic threshold, nor in symptom scores. Thus, the

clinical relevance of this finding remains to be established. Recently, two studies have been performed (AFFIRM, RACE) suggesting that a rate control might be acceptable at least for some patients, but this has not been proven for dronedarone. In the NfG on Antiarrhythmics (CPMP/EWP/237/95) it is stated explicitly that if the claimed indication is slowing the ventricular rate of the arrhythmia, it may be sufficient to demonstrate a significant reduction of morbidity and symptoms. This is provided that no negative effects are shown on life expectancy in high-risk patients, which is not the case as shown by the data of the ANDROMEDA study, which will be discussed in the safety section! Currently, verapamil, beta-blockers, sotalol and amiodarone are being used for this indication, but comparative data are lacking. The data of the ERATO study do show additive effects to some of these agents, but specific data are lacking.
In summary, as no clinical benefit has been demonstrated and comparative studies not been performed, dronedarone cannot be accepted for this part of the indication. This is also considered a major objection.

III.3.4 Clinical safety

Safety issues in the targeted AF/AFL patient population are pooled across all patients with AF/AFL (DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ ERATO). This is possible because of the consistency of results across the AF/AFL studies. A total of 1,681 patients were randomized and treated in studies conducted in the claimed indications, 564 in the placebo group and 1,117 patients in the dronedarone group. In total 989 patients started with the recommended dose of 400 mg BID but only 283 were exposed for 360 days. A smaller number of patients was for a shorter period exposed to 600 and 800 mg BID dose regimens. The age range of patients using the 400 mg BID was between 20-88, with almost half of patients younger than 65 years and around 16 % over 75 years in the AF/AFL population and approximately 70% male patients. Therefore, the safety data-set is based on a fair representation of the AF/AFL population seen in clinical practice. Extrapolation of safety information to other racial groups than Caucasians is not possible, due to only minimal (~1%) inclusion of such patients. Patients with relatively mild cardiovascular comorbidity were included in the AF/AFL study population. High risk patients, such as patients with CHF III-IV and patients with severe ventricular arrhythmias in need for antiarrhythmic treatment were excluded from these studies. Instead, these patients were studied in study EFC4966/ANDROMEDA consisting of 627 patients with a recent hospitalization for a severe symptomatic episode of CHF (NYHA class III or IV) and with LVEF≤35%, and study DR13151/LTS3841 in 116 patients with ventricular arrhythmias in whom an ICD was implanted.

Safety in AF/AFL population
Over 60% of all patients reported any adverse events (AEs) in the AF/AFL population. Treatment emergent adverse events (TEAEs) were dose-dependent, 60% in the placebo group vs. 67% and 73 % for the 400 mg BID and 800 mg BID dronedarone groups, respectively. Female sex and older age were found to lead to more frequently reported TEAEs, which could theoretically be explained by higher exposure as observed in the pharmacokinetics studies. The applicant should discuss the possibility of special dose recommendations in these patient groups.
In the system organ classes (SOCs) with TEAEs > 10% there was a dose response in the GI disorders (diarrhoea), investigational abnormalities (QT-prolongation and increased blood urea) and cardiac disorders (bradycardia, palpitations and atrial tachycardia). When the clinically used dose of 400 mg BID was assessed, increases in TEAEs compared to placebo were observed in some of the investigations, particularly increase in serum creatinine (2.2% vs. 0.2%), or as skin and subcutaneous tissue disorders (9.5 % vs 6.4), psychiatric disorders (5.3% vs 2.8 %) and blood and lymphatic disorders system organ classes 1.4% vs 0). Additionally, incidences of back pain (3.3%), arthralgia (3.1%), upper respiratory tract infections (2.9%), epistaxis (1.7%), urinary tract infection (1.5%), joint swelling (1.3%), vertigo (1.3%), eczema (1.0%) and anemia (0.7%) were increased in the dronedarone 400 mg BID group compared to the placebo group.
Among the most frequent cardiac TEAEs cardiac arrhythmias (5.7% vs. 4.6%) and heart failures (2.4% vs. 1.1%) did not differ significantly between dronedarone 400 mg BID and placebo groups. No TdPes de pointes were reported. The rates of thyroid (overall 1.6% versus 1.3%; mainly hypothyroidism 0.2% vs 0.9%, placebo and dronedarone resp.), and vision disorders were low and not

clearly different between the two treatment groups. Photosensitivity rash and reactions were reported in few (0.8%) patients treated with dronedarone 400 mg BID. Interstitial or alveolar pneumonitis, another typical amiodarone-related TEAE, seems also uncommon with dronedarone. Cough and dyspnoea were frequently reported.

In general, **serious adverse events** occurred to a similar extent in placebo (14%) and actively treated (13%) groups. This holds also true for the most frequently reported serious AEs of cardiac disorders (e.g. cardiac arrhythmias). However, within this group of cardiac disorders heart failures were more commonly reported in the dronedarone 400 mg BID group. The second most frequently reported serious TEAEs were within the gastro-intestinal organ class. Especially GI haemorrhages occurred more frequently in the dronedarone 400mg BID dose group (0.6%) than in the placebo group (none). This was justified by the applicant on the basis that these patients were concomitantly prescribed an oral anticoagulant. Combined with the increased finding of TEAEs epistaxis and anemia in the dronedarone treatment group, an increased bleeding tendency cannot be excluded. Hypersensitivity reactions do not seem to be a major concern, only two cases of anaphylactic reactions were reported only.

Incidences of patients with potentially clinical significant renal abnormalities (creatinine, creatinine clearance) were dose dependent and higher in all dronedarone dose groups compared to placebo. With the recommended therapeutic dose of 400 mg BID, mean increases in serum creatinine were mild to moderate (approx. 10 µmol/L), dose-dependent and observed consistently in all patients with AF/AFL. A maximal change of ≥ 30% in serum creatinine levels relative to baseline levels was observed in 16% of patients receiving dronedarone 400 mg BID. These increases were observed by Day 5 (day of first assessment on treatment), values remained stable during treatment, and returned rapidly to baseline level after the end of treatment in ERATO and DAFNE study populations, but less clear in the EURIDIS/ADONIS population.

Apart from renal dysfunction special analysis was made of ECG changes. In the main confirmatory studies EFC3153/EURIDIS and EFC4788/ADONIS, bradycardia as defined by HR≤ 50 bpm and decrease ≥ 15 bpm occurred in 10.4% vs. 5.6% of dronedarone vs placebo treated patients. Prolongation of PR-interval and QTcB-interval (≥ 500 ms: 5.9% vs. 2.2% and increase > 60 ms 14.2% vs. 5.5% in dronedarone vs placebo treated patients) was more frequently reported with dronedarone than with placebo. This led to more frequently reported (≥1) postbaseline PCSA in 12-lead ECG parameters in this patient group. No TdPes de pointes were reported during these studies. A dose effect was observed on the PR and QTc intervals. This was reflected clinically in an increased incidence of bradycardia and heart block TEAEs in the highest dose of 800 mg BID. Of note all QTc assessments are done only by the Bazett's whereas correction for heart rate by Fridiricia would have been appropriate and in accordance with the current ICH guideline on QT prolongation.

No specific safety issues in the clinical studies were identified in the AF/AFL population using co-medication, including beta-blockers and calcium antagonists. Two cases of serious digitalis intoxication were noted.

Study drug was discontinued in 10% of patients in the clinically relevant dronedarone 400mg BID dose group compared to 6% in the placebo group. This was driven by gastrointestinal disorders, investigations, cardiac disorders, nervous system disorders and skin and subcutaneous tissue disorders. Renal and urinary tract investigations (0.7% vs. 0%), cardiac arrythmias (1.2% vs. 0.7%), epidermal and dermal conditions (1.2% vs. 0.4) and general system disorders (0.7% vs. 0.2%) were events that led to > 0.5% difference in permanent withdrawal of study medication between dronedarone 400 mg BID and placebo groups. ECG changes did not lead to a significant study drug discontinuation.

Patients with AF/AFL had a similar 1% chance of death within the planned study-period (6 months for ERATO/DAFNE and 12 months EURIDIS/ADONIS) in placebo and 400 mg BID treatment. Such a mortality rate is not unexpected in this particular patient population, and not surprisingly deaths were primarily attributed to sudden deaths and cardiovascular causes. More patients died though while on treatment in the dronedarone 400 mg BID group (0.9% [95%CI 0.1% - 1.5%]) than in the placebo group (0.5% [95%CI: 0.4% - 1.7%]). After study treatment was discontinued, mortality rates leveled out between treatment and placebo groups.

Safety in special patient populations

Study EFC4966/ANDROMEDA aimed to explore the potential clinical benefit of dronedarone 400 mg BID treatment versus placebo for reducing death or hospitalization for worsening heart failure in

patients with a recent hospitalization for a severe symptomatic episode of CHF (NYHA class III or IV) and with LVEF ≤35% when added on-top of treatments for CHF. The rationale was that dronaderone's anti-arrhytmic properties could have clinical benefits in patients with CHF. Both patients with AF/AFL and without were included. Seven months after randomization of the first patient, the study was discontinued. Analysis of adjudicated causes of death had demonstrated a greater proportion of patients in the dronedarone group with worsening CHF (40%) as the primary cause of death compared to the placebo group (17%). This occurred early after treatment. No proarrhythmic effects were observed. Observed increases in serum creatinin levels in the dronedarone treatment arm may have led investigators to discontinue ongoing or not initiate treatment with ACE inhibitors or AII receptor antagonists (ARBs). Although, ARB or ACE-inhibitor use is recommended in this patient population. Post-hoc analysis, then demonstrated a strong association between the withdrawal of ACE-inhibitors and ARBs and the incidence of death. However, only 14/41 of the patients who withdrew their medication had higher blood creatinine levels or renal impairment and it is not clear what happened in the other 27 cases. An unplanned evaluation after 6-months after study termination showed that the number of deaths levelled out in both groups, 39 (placebo) versus 42 (dronedarone).
Study DR13151/LTS3841 aimed to explore whether dronedarone interacted with the function of the ICD. No such interaction was observed. In fact, there was trend for fewer appropriate ICD interventions under dronedarone treatment.

In summary, dronedarone in its recommended dose of 400 mg BID is reasonably well-tolerated, taking into account its AEs profile in relation to the other tested dosages and placebo. GI disorders are dose dependent and may lead to discontinuation. An increased bleeding tendency cannot be excluded. Dronedarone's safety profile seems favourable when comparison is made for the well known toxic effects of amiodarone, but nervous system and skin disorders have been observed. Lack of a consistent effect on thyroid function, obviating the need for systematic monitoring is a clear advantage. Effects on creatinine levels and cardiac conduction and repolarisation (QTc) deserve special attention.

Increase in **serum creatinine** is considered a major safety issue. In the ANDROMEDA trial this led to discontinuation of vital drug therapy, which in turn may have led to the observed increased mortality in the dronedarone treatment group. In clinical practice this may lead to similar problems. Also a valuable clinical parameter for renal function is lost. Long-term data is not available. Part of the effect on serum creatinine may be explained by decrease in tubular secretion . Also, transport of other cations may be affected as well and interactions may be present with other drugs (or contrast agents) that are secreted by the renal tubule and this needs further exploration.
Dronedarone slows AV-conduction and prolongs repolarisation, effects that may increase with dose. Based on its electrophysiological profile **ECG effects** can be expected, but their magnitude is difficult to estimate in terms of pro-arrhythmic potential, in particular because comparison with other class III anti-arrhythmics is lacking. This is considered to be a major objection. Correction of the QT-data by Fridericia is warranted and more safety data to rule out pro-arrhythmic effects should be submitted.
Clinically relevant interactions were limited, but data were obtained under well controlled conditions. The issue is whether this can be managed in daily practice.

The safety of dronedarone in terms of **life expectancy** has not been established. Excess mortality in the dronedarone 400 mg BID versus placebo treatment arm in patients with symptomatic CHF with LVEF <35% was observed, in particular in the early months after start of treatment. This cannot fully be explained by the increase in patients who discontinued ACE-inhibitors or ARBs and warrants further controlled data on morbidity and mortality. The CHMP/EWP/237/95 Note for Guidance on anti-arrhythmic drugs (item 4.8) stipulates that for drugs with a proposed indication of rate or rhythm control in AF patients no trend of reduced life expectancy should be demonstrated. Sudden death has also been reported in other clinical studies. Marketing authorization cannot be granted as long as data from the study EFC5555/ATHENA (which started in June 2005) in the intended AF/AFL population with a clinical endpoint including mortality are not available. Also, a risk management plan (RMP) should be implemented to minimise risks of interactions and co-morbidity.

IV. BENEFIT RISK ASSESSMENT

Dronedarone is indicated for rhythm and rate control in patients with AF/AFL, to maintain sinus rhythm or to decrease ventricular rate. Dronedarone demonstrates electro-physiological characteristics belonging to all 4 Vaughan-Williams classes of antiarrhythmic compounds. These characteristics are in line with amiodarone, another anti-arrhythmic agent, which has been shown to be one of the most effective agents for this indication, but also one of the most toxic. A safer alternative for amiodarone with similar efficacy could therefore certainly be an advantage. Whether this is the case for dronedarone remains undetermined.

Dronaderone an even more complex interaction potential than amiodarone, being both a substrate and an inhibitor of CYP P450 enzymes, including CYP3A4, that can lead to major problems in daily practice. The clinical trials submitted did show that dronedarone in a dose of 400 mg BID can significantly prolong median time to AF recurrence by approximately 50 days and reduce incidence of AF after 12 months by approximately 10%. In patients with AF ventricular rate decreased by 10-12 bpm at rest up to 31 bpm at maximal exercise. Whether these findings can be considered as surrogate for clinical benefit remains to be established. No clinical benefit in terms of improvement in symptoms or exercise testing could be shown in patients who showed rate control. No comparison was made with amiodarone and/or other antiarrhythmics that are currently used for rate or rhythm control. Dronaderone's altered pharmacokinetics compared to amiodarone can certainly affect not only safety, but also efficacy. Patients with atrial flutter were not included in the studies.
Safety data indicate that tolerability was acceptable, although GI symptoms did occur dose-dependently. Amiodarone-like extracardiac toxicity, in particular at the thyroid or pulmonary level did not occur, which could potentially be an advantage. Both an increase in serum creatinine and/or differences in long term outcome, however, could negate this advantage. Although increase in serum creatinine might in part be related to inhibition of tubular secretion of creatinine, this may affect the management of the patients negatively, as creatine levels cannot be used as a marker for renal function. Similar to amiodarone, ECG effects can occur, including prolongation of the PR-interval and QTc, which may also affect outcome. One survival study was carried out in patients with a recent hospitalization for a severe symptomatic episode of CHF (NYHA class III or IV) and with LVEF ≤35%II-IV with a negative effect on mortality. Although differences in management, in particular regarding co-medication of ACE-inhibitors and AII receptor blockers could be one explanation, it cannot be ruled out that other causes may have also contributed.

Finally, the absence of dosing alternatives to the investigated 400 mg BID reduces the clinical potential of dronedarone. Higher exposure may lead to reduction of efficacy while safety risks increase. In the DAFNE study no significant effect was observed in the 600 mg BID group, which remains unexplained. This can occur in special patient groups, like elderly females, and during concomitant medication and may negatively influence the benefit/risk profile.

In summary, the dossier of dronedarone is limited and its submission can be considered premature. As required by NfG on antiarrythmics (CPMP/EWP/237/95), comparative data are for an appropriate assessment of benefit and risk. Comparative data with other antiarrhythmics will allow better assessment on the clinical relevance of the effects on rhythm and rate control and also on various safety aspects, in particular EKG effects. Placebo or actively controlled safety data are necessary to allow a final assessment on the effect on morbidity and mortality. A study EFC5555/ATHENA evaluating the efficacy of dronedarone 400 mg BID versus placebo for the reduction of cardiovascular hospitalization and death in a population of elderly or high risk patients with AF/AFL started in June 2005. Results need to be awaited. At the moment, the ratio between efficacy and safety is considered negative.

This Withdrawal Public Assessment Report is based on the Day 120 assessment report, which is the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the marketing authorisation application. This Withdrawal Public Assessment Report does not include all available information on the product as the CHMP assessment of the applicant's responses to Outstanding Issues raised by CHMP was still ongoing.
It should therefore be read in conjunction with the Questions and Answers Document on the withdrawal of the marketing application for this product, which provides an overview on all available information on the product at the time of the Applicant's withdrawal.

V. RISK MANAGEMENT PLAN

The risk management (RMP) was submitted with the answers of the applicant to the day-120 comments.