



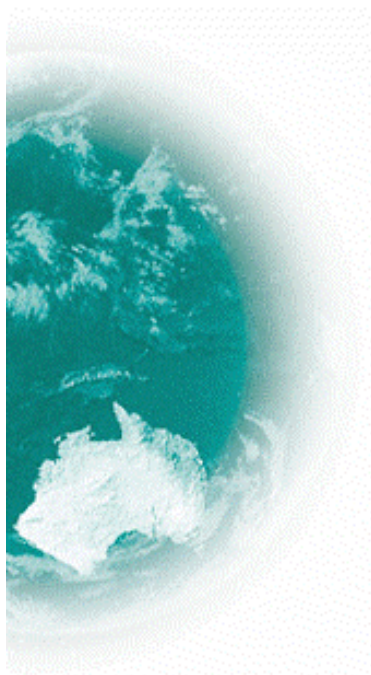
**Australian Government**  
**Department of Health and Ageing**  
**Therapeutic Goods Administration**

**Australian Public Assessment Report  
for  
Dronedarone Hydrochloride**

**Proprietary Product Name: Multaq, Dronedarone Winthrop,  
Dronedarone Sanofi**

**Submission No: PM-2008-3045-3**

**Sponsor: Sanofi Aventis Australia Pty Ltd**



***October 2010***

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## **I. Introduction to Product Submission**

### **Submission Details**

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	19 July 2010
<i>Active ingredient(s):</i>	Dronedarone hydrochloride
<i>Product Name(s):</i>	Multaq, Dronedarone Winthrop, Dronedarone Sanofi
<i>Sponsor's Name and Address:</i>	Sanofi-Aventis Australia 12-24 Talavera Road Macquarie Park NSW 2113
<i>Dose form(s):</i>	Film coated tablets
<i>Strength(s):</i>	400 mg
<i>Container(s):</i>	PVC//Al blister packs and HDPE bottles
<i>Pack size(s):</i>	20, 50, 60, 100, 200 and 500 tablets
<i>Approved Therapeutic use:</i>	To reduce the risk of cardiovascular hospitalisation in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors, who are in sinus rhythm or who will be cardioverted, on top of standard therapy.
<i>Route(s) of administration:</i>	oral
<i>Dosage:</i>	400 mg twice daily with meals
<i>ARTG Number (s):</i>	156356, 156373, 156374, 156379, 156385, 156386

### **Product Background**

Dronedarone is a benzofuran derivative that has been developed to overcome the use limiting iodine-associated adverse effects of the commonly used antiarrhythmic drug, amiodarone, with which it is structurally related. Dronedarone inhibits transmembrane  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ , and L-type calcium currents and is also an antagonist at alpha- and beta-adrenoceptors but, unlike amiodarone, has little effect at thyroid receptors. It is one of a number of analogues of amiodarone being developed with the aim of avoiding the significant extracardiac side effects of amiodarone itself.

Dronedarone was developed as an anti-arrhythmic agent for the first line treatment of atrial fibrillation and atrial flutter. It is structurally related to amiodarone but lacks the iodine component. It exhibits electrophysiological properties from all four Vaughan-Williams classes of antiarrhythmic agents with multiple ion channel blocking including inhibiting potassium currents (Class III), sodium currents (Class Ib) and calcium currents (Class IV). It also on-competitively antagonises beta adrenergic activity (Class II). It is less lipophilic than amiodarone, has a much smaller volume of distribution, and has an elimination half-life of about 24 hours, which contrasts to amiodarone's half-life of several weeks. As a result of these pharmacokinetic characteristics, dronedarone dosing is said to be less complicated than with amiodarone.

Treatments used for rhythm control in atrial fibrillation (AF) include electrical cardioversion or drug conversion using amiodarone, flecainide or sotalol. Atrial flutter generally uses electrical

cardioversion and similar pharmacotherapeutics. Treatments used for rate control include digoxin, atenolol, metoprolol, diltiazem and verapamil. Treatment for thromboembolic complications involves anti-coagulation.

The proposed tablets contain 400 mg dronedarone present as the hydrochloride salt, are film coated and are not scored. The maximum daily dose is 800 mg given as 1 tablet in the morning and 1 in the evening, with meals. There are three proposed trade names containing dronedarone (Multaq, Dronedarone Sanofi and Dronedarone Winthrop) but the product will be referred to as Multaq for the remainder of this AusPAR. Multaq is indicated in patients with a history of, or current atrial fibrillation or atrial flutter, for the reduction of the risk of cardiovascular hospitalisation.

## Regulatory Status

Dronedarone has been approved in the USA in July 2009, Canada in August 2009, Switzerland in September 2009 and the European Union in November 2009. The data submitted in the USA, Europe and Canada are the same as the dataset in this submission and the submission has not been withdrawn, rejected or deferred in any country.

### USA Approved Indication:

Multaq is indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (that is, age >70 years, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter  $\geq 50$  mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted [see *Clinical Studies*].

### Canada Approved Indication:

Multaq is indicated for the treatment of patients with a history of, or current atrial fibrillation to reduce the risk of cardiovascular hospitalization due to atrial fibrillation (see Clinical Trials).

### Europe Approved indication:

Multaq is indicated in adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate (see section 5.1).

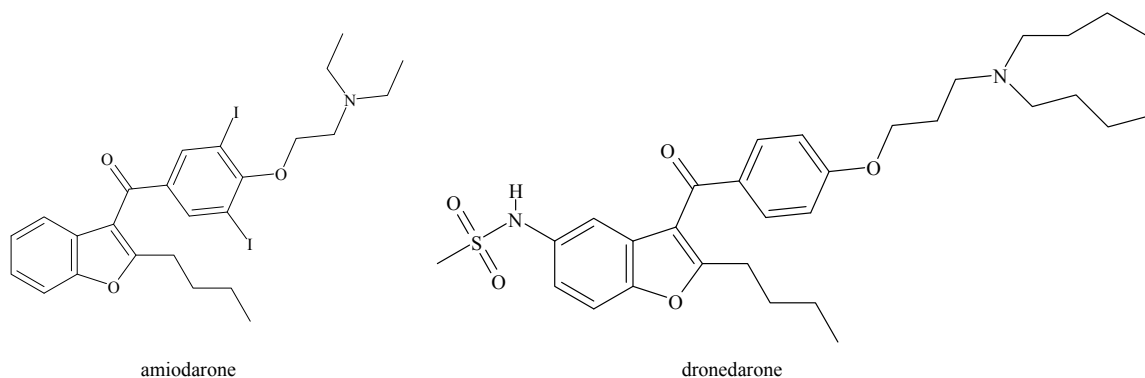
## Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

## II. Quality Findings

### Drug Substance (active ingredient)

Dronedarone hydrochloride is a new chemical entity which is related to amiodarone. See structures below. It is achiral. It contains a sulphonamide functional group.



### **dronedarone hydrochloride**

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

Formula = C<sub>31</sub>H<sub>44</sub>N<sub>2</sub>O<sub>5</sub>S.HCl

MW = 593.22 (salt), 556.76 (free base)

CAS No. = [141625-93-6] (salt), [141626-36-0] (free base)

pKa = basic function: 9.40 – acidic function: 9.46

melting point 141.2°C

solubility (practically insoluble) = aqueous

pH 1.2

citrate pH 2

phosphate pH 7

0.64 mg/mL

<0.01 mg/mL

< 0.01 mg/mL

<0.01 mg/mL

0.064%

< 0.001%

<0.001%

<0.001%

Only one polymorphic form has been found. As can be seen from above, the solubility is greater in water than in buffers, but in all cases it is practically insoluble.

The specifications of dronedarone hydrochloride drug substance include:

- Satisfactory limits for assay (98.0-101.5%) and related substances (including a limit of not more than [NMT] 0.2% for a metabolite of dronedarone and with all other impurities limited to International Conference on harmonisation [ICH] identification threshold of NMT 0.10%).
- There were a number of potential genotoxic substances used as intermediates in the synthesis or produced as by-products to the synthesis. These were tested for and all were present in amounts of < 1 ppm. The Medicines Toxicology Evaluation Section of the TGA's Office of Prescription Medicines (MTES) was satisfied that the levels present (< 0.8 µg/day) were acceptable.
- Due to the poor solubility at some physiological pHs, the particle size distribution is tightly controlled.
- The residual solvent limits were below limits allowed by ICH guidance.

### **Drug Product**

The drug product is to be manufactured by Sanofi Winthrop Industrie, France. The tablets include poloxamer 407 as a solubilising agent. This polymer decreased the food effect observed with earlier formulations. The current GMP Clearance for this site expires on 13 June 2009, and the company is in the process of having this updated. Manufacture is by a typical wet granulation process followed by film-coating. The drug product is well controlled with satisfactory expiry limits for assay (95.0-105.0%) and degradants (NMT 0.2% for any individual<sup>1</sup> and NMT 0.5% in total). The dissolution is slow for an immediate release tablet and the company has ensured that the dissolution is consistent by imposing a two stage dissolution test.

Stability data were provided to support the proposed shelf life of 3 years when stored below 30°C in both opaque PVC//Al blister packs and white HDPE bottles. The pack sizes (see title) allow for a large number of tablets in one pack. These were brought to the attention of the Delegate.

The chemistry and quality control aspects of the draft PIs have been finalised to the satisfaction of the quality evaluator.

### **Bioavailability**

A large number of differing capsules and tablets were formulated during the development of the proposed tablets.

As early studies indicated that food markedly increased the bioavailability of dronedarone, studies were conducted to minimise this effect. These studies resulted in the inclusion of poloxamer 407 in the formulation (formulation 1C1), which caused a reduction of the food effect from 23-fold for

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<sup>1</sup> The ICH qualification limit for drug substances with a maximum daily dose of 60 mg is 0.333%

tablets without the surfactant to 4-fold. This formulation was optimised, resulting in formulation 2E2, a 200 mg film coated tablet that was used in dose ranging studies. A further study was conducted using formulation 2E3, which differed from 2E2 in strength, shape, engraving and milling of the drug substance, but was otherwise qualitatively and quantitatively very similar.

The tablets proposed for registration, 2E5, differ only in engraving from tablets 2E3. These two tablets have equivalent dissolution profiles. The sponsor has argued that, given this close similarity, no *in vivo* bioequivalence study was needed to compare the two formulations. This was accepted.

No further food studies were conducted after the effect of food was established on formulation 1C1 because of the similarity of the core formulations. Since the tablets were given with a meal in the clinical efficacy/safety studies, it is recommended that the PI states that tablets be taken with a meal (this is the case).

Seven bioavailability studies were included in the submission. A number of these were considered irrelevant to the proposed formulation and either not evaluated or only briefly summarised by the quality evaluator.

**Study Ppk2937:** determined the absolute bioavailability of a 100 mg capsule (dose 800 mg) in comparison to a 1 mg/mL intravenous (IV) injection (dose 60 mg infused over 1 hour). It also determined the effect of food on the capsule. As the capsule is not proposed for registration, the study was only summarised. The absolute bioavailability in the fed state was 15% and food increased the bioavailability by 7.5-fold. The total clearance after IV administration was  $176 \pm 34$  L/h.

**Study Gar3144:** compared the bioavailabilities of four different formulations at a dose of 800 mg (200 mg capsule 2B1, 200 mg semi-solid capsule 001, 200 mg semi-solid capsule 002 and 200 mg semi-solid capsule 003). It also investigated the effect of food on these formulations. As none of the formulations were relevant to the formulation proposed for marketing, this study was not evaluated.

**Study Bdr2889:** compared the bioavailabilities of four different formulations at a dose of 800 mg (200 mg capsule 2B1, 400 mg tablet with various percentages of poloxamer in granulation solution 1B1, 1C1 and 400 mg 'Simplex' tablet 1A1). It also investigated the effect of food on these formulations. As none of the formulations were used in the Phase III clinical trials or are that proposed for registration, this study was only summarised. This study indicated that the bioavailability was maximised (and the effect of food minimised) with the 1C1 tablet.

**Study Ali3179:** determined the effect of food (high fat vs low fat vs fasting) on a 400 mg tablet (dose 800 mg) that contained poloxamer in granulation solution (1B1). As the tablet formulation was not used in the Phase III clinical trials nor is that proposed for registration, this study was only summarised. The sponsor concluded that low and high fat meals significantly increase the bioavailability of dronedarone, with a 'slightly higher food interaction for the high fat meal'.

**Study Ali3180:** determined the effect of food (high fat vs low fat vs fasting) on a 400 mg tablet (dose 800 mg) that contained poloxamer in the granulation solution (1C1). As the tablet formulation was not used in the Phase III clinical trials nor is that proposed for registration, this study was only summarised. Again the sponsor concluded that low and high fat meals significantly increase the bioavailability of dronedarone, with a 'slightly higher food interaction for the high fat meal'.

**Study Gar3585:** compared the bioavailabilities of four different formulations at a dose of 800 mg (400 mg tablet with slow dissolution 1E2/F19, 400 mg tablet with medium dissolution 1E2/F18, 400 mg tablet with fast dissolution 1E2/F17 and 400 mg tablet reference F16/1C1). It also investigated the effect of food on these formulations. The three 1E2 formulations contain the same tablet core as the tablets used in the Phase III clinical trials and as proposed for marketing. Each has

a different grade of granulate in that the water content was different. This study was evaluated in full. After evaluation, it was concluded that this study was not directly relevant to the tablets proposed for registration, but was a valuable study in the development of the proposed tablets: the results did not show significant differences in bioavailability from the different granulates, whereas the dissolution results were very different indicating a very discriminative dissolution test method.

**Study Bdr4680:** compared the bioavailability of the 400 mg tablet used in the Phase III clinical trials (2E3) to the bioavailability of the 200 mg tablet used in the Phase II clinical trials (2E2) both co-administered with a 100 mg capsule containing <sup>13</sup>C-dronedarones such that the dose was 800 mg. This study was evaluated in full. The two tablets were bioequivalent under the fasting conditions used in this study.

### *Conclusions*

Neither the absolute bioavailability nor the bioavailability relative to an oral solution of the tablets proposed for registration has been established in the submission. Given that the clearance determined in study Ppk 2937 (176 L/h) is not within the range quoted in the PI (130-150 L/h), it would not be expected that the absolute bioavailability of dronedarone from the capsules administered in this study would be indicative of that from the registration tablets.

It is also noted that the food effect on the bioavailability of dronedarone was minimised in studies not involving the registration formulation and that comparison of the Phase II and Phase III tablets in study Bdr4680 was done in the fasting state, whereas the tablets are to be administered with food. There was no study comparing the proposed 2E5 tablets or phase III tablets taken with and without food. However, there is unlikely to be any difference in the bioavailability of 2E3, 2E4 and 2E5 tablets given their qualitative and quantitative identity and the closely similar dissolution profiles.

These facts were brought to the attention of the Delegate in relation to finalising the PI.

This application was presented to the 125th meeting of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC) where no objections were raised in relation to chemistry, quality control or the bioavailability studies provided.

### **Quality Summary and Conclusions**

Approval of this submission is recommended with respect to chemistry, quality control and bioavailability.

The following facts were brought to the attention of the Delegate for consideration:

- That dronedarone is a sulphonamide.
- That some pack sizes are large (up to 500 tablets).
- The current GMP Clearance for the site that manufactures the tablets was due to expire on 13 June 2009.
- That details in the pharmacokinetic section of the draft Product Information document were not necessarily supported by the bioavailability data provided.

## **III. Nonclinical Findings**

### **Introduction**

The nonclinical submission was adequate overall, although many studies were dated, with toxicokinetic data sometimes being absent or not available at appropriate doses. With one exception, safety pharmacology studies were not compliant with Good Laboratory Practice (GLP).

## Pharmacology

### Primary pharmacodynamics

The pharmacological effects of dronedarone were extensively investigated, in terms of haemodynamic/electrocardiogram (ECG) activity and mode of action, but *in vivo* investigation of efficacy for the intended indication (atrial fibrillation or flutter) was limited. In an atrial pacing/vagal stimulation model in anaesthetised dogs, dronedarone effectively terminated atrial fibrillation (AF) and induced resistance to AF re-induction, as did amiodarone. However, intravenous (IV) administration was used (2.8 mg/kg followed by 9.4 mg/kg in cases of no response) and plasma concentrations following the 10 minute infusions used were unknown.

However, the anti-arrhythmic activity of dronedarone was shown in several other models (ventricular fibrillation), mainly in rats but also in dogs and pigs, with amiodarone generally being less effective where this was also tested. These studies included oral administration and an effective single dose of 84.5 mg/kg in rats was associated with plasma concentrations of about 0.22 µg/mL, which was slightly above the clinical maximal plasma concentration ( $C_{max}$ ) of 0.15 µg/mL, while 11.7 mg/kg/day was effective in pigs.

*In vitro* and *in vivo* studies showed that the N-debutylated metabolite SR35021 generally exhibited similar activity to dronedarone but was less potent (approximately 2-10 times less potent than the parent compound), while the O-propanoic acid derivative SR90154 showed little or no activity. For example, reperfusion-induced ventricular fibrillation in anaesthetised rats was reduced to similar extents by 2.8 mg/kg of dronedarone and 9.3 mg/kg of SR35021, but not by 30 mg/kg of SR90154 (IV), although these doses all reduced heart rates and blood pressures.

Dronedarone pro-arrhythmic activity was only occasionally observed, notably with programmed electrical stimulation in post-myocardial infarction dogs, in which 3 IV doses of 2.8 mg/kg resulted in the promotion of induced ventricular tachycardia with progression to fibrillation. Additionally, a literature publication reported the occurrence of torsades de pointes in dogs with complete AV block and acquired long QT-syndrome after dronedarone but not amiodarone treatment (van Opstal *et al.*, 2001).<sup>2</sup> Only single oral dose levels were investigated, with a plasma dronedarone concentration at least 8x a human  $C_{max}$  of 0.15 µg/mL being recorded (1.3 µg/mL at an unstated time). The significance of these findings is not clear, but torsades de pointes have been reported with amiodarone use.

### Mode of action

Most antiarrhythmic drugs are ion channel blockers affecting the cardiac action potential, and dronedarone exhibited characteristics of the four main classes in the widely used Vaughan-Williams classification. *In vitro* it primarily blocked the outward  $K^+$  currents involved in cardiac repolarisation (class III effect), including  $I_{Kr}$ ,  $I_{Ks}$ ,  $I_{Kur}$  and  $I_{K(Ach)}$  with the latter showing the highest affinity (median inhibitory concentration [ $IC_{50}$ ] value of about 0.01 µM in guinea pig atrial cells). Inhibition of  $Ca^{2+}$  and  $Na^+$  currents (respectively class IV and class I effects) was also shown, and dronedarone exhibited  $\alpha$ - and  $\beta$ -adrenergic activity antagonism *in vivo* (class II effect, adrenaline and isoprenaline agonists), even though *in vitro* receptor binding was poor.

### Safety and secondary pharmacology

Safety pharmacology studies were adequate in terms of studies conducted and oral doses used, although as noted above they were generally not GLP-compliant. Besides standard investigations

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<sup>2</sup> van Opstal *et al.* Chronic amiodarone evokes no torsades de pointes arrhythmias despite QT lengthening in an animal model of acquired long QT-syndrome. *Circulation* 2001; 104: 2722-2727.



of central nervous system (CNS), cardiovascular, renal and gastrointestinal (GI)-tract effects, special studies also examined effects on thyroid hormones (see *General toxicity* for discussion) and phospholipidosis in male rats treated orally for 2 weeks. Dronedarone had no effect on liver and lung phospholipids, unlike amiodarone which elicited significant increases, although phospholipidosis was a feature of the toxicity studies; it is noteworthy that amiodarone plasma concentrations at 24 hours after the last dose were higher than those for dronedarone.

CNS, respiratory (guinea pig), renal and GI-tract changes were minor or occurred at high doses. A substantial reduction in rat gastric emptying was seen at 300 mg/kg, but not at 100 mg/kg, which probably accounts for stomach and small intestinal distension seen at necropsy in a two week rat toxicity study. Rat urinary values were measured after single (30-100 mg/kg) and repeated (10-30 mg/kg/day x 2 weeks, males only) oral administration, but it was difficult to determine any consistent effect of treatment especially when compared with urinalysis results from the two week toxicity study (30-160 mg/kg/day). Haematuria and proteinuria seen after IV administration were probably related to the use of a macrogol 400 vehicle, which resulted in vehicle- and dronedarone-induced haemolysis *in vitro* (see *Local tolerance*), and there were no urinalysis findings in a 4 week IV toxicity study using a different vehicle. Several cardiovascular responses were seen after IV and intra-duodenal administration to anaesthetised dogs, as may be expected, although these were not the intended routes and the rationale for the use of the latter was not clear. The significance of the observed increases in respiratory rate and flow is uncertain, especially as there were no vehicle controls. There were no respiratory changes in the guinea pig study, although achieved plasma concentrations were not particularly high (about 230 ng/mL at 2 hours with the highest dose (HD) versus human C<sub>max</sub> values of about 85-150 ng/mL).

No specific secondary pharmacology studies were conducted, except for *in vitro* assessment of binding to dopamine receptors which showed 30-33% inhibition with 10 µM dronedarone (D1 and D2L subtypes) or IC<sub>50</sub> values of 1.1 µM (D3) or 4.2 µM (D4.2). These data were included in the sponsor's Nonclinical Overview, but not in a study in the sponsor's Nonclinical dossier. Such interactions may be involved in the elevations in prolactin observed in mice (see *Genotoxicity and carcinogenicity*).

## **Pharmacokinetics and Relative Exposures**

Following single IV administration at doses of 1-10 mg/kg, plasma dronedarone clearance values were slightly higher in rats (4.1 L/h/kg) than in dogs and humans (respectively 1.8-2.4 and about 2.2 L/h/kg). The highest value was in cynomolgus monkeys (4.9 L/h/kg) although this species was used only for one minor toxicity study. Oral bioavailability was low in rats and dogs (20-27%) as in humans (15%).

Dronedarone exposures achieved in the oral toxicity studies were adequate in mice and dogs, but were relatively low in rats, as tabulated below, and characterised by greater than dose-proportional increases (Table 1). Dosing was once daily compared with the proposed twice daily (bd) regimen in humans. There were no differences between experimental species and humans for plasma protein binding, as assessed *in vitro*, which was almost complete (>99%). This also applied to the N-debutylated metabolite SR35021 (>98%) which was also measured in the toxicity studies. Assays with human serum albumin and α1-acid glycoprotein showed that both compounds bind mainly to albumin.

Table 1: Toxicity details

Species	Duration (weeks)	Dose (mg/kg/day)	AUC <sub>0-24 h</sub> (µg.h/mL) and sample day/week <sup>#</sup>	Exposure ratio (ER) <sup>&amp;</sup>	
				Dronedarone	SR35021
General toxicity					
Mouse	13	50, 150, 450	0.50, 5.0, 20.4 (wk 13) (0.62, 6.6, 29.5) <sup>†</sup>	0.3, 2.9, 11.9	0.4, 4.4, 19.7
Mouse	104*	75, 150, 300	1.7, 5.6, 13.4 (wk 52) (1.6, 6.5, 15.1) <sup>†</sup>	1.0, 3.3, 7.8	1.1, 4.3, 10.1
Rat	13	5, 17.5, 60	-, 0.62, 4.7 (d 30 + 90) <sup>††</sup> (-, -, 1.1) <sup>††</sup>	-, 0.4, 2.7	-, -, 0.7
Rat	26	2, 10, 50	-, 0.35, 3.8 (wk 5 + 28) <sup>††</sup> (-, -, 0.95) <sup>††</sup>	-, 0.2, 2.2	-, -, 0.6
Rat	104*	5, 25, 70	0.12, 2.0, 8.8 (wk 13 + 52) (0.02, 0.63, 3.0)	<0.1, 1.2, 5.1	0.01, 0.4, 2.0
Dog	13	5, 17.5, 60	-, 2.8, 44.8 (d 35 + 97) (-, 0.33, 3.3)	-, 1.6, 26.2	-, 0.2, 2.2
Dog	52	5, 15, 45	-, 2.4, 25.0 (d 30 + 188 + 366) (-, -, 1.5) <sup>††</sup>	-, 1.4, 14.6	-, -, 1.0
Reproductive toxicity					
Rabbit <sup>\$</sup>	2	20, 60, 200	0.061, 0.53, 13.85 (d 13) (0.016, 0.22, 11.02)	<0.1, 0.3, 8.1	0.01, 0.1, 7.3

# values in ( ) refer to SR35021, \* carcinogenicity studies & AUC<sub>0-24 h</sub> relative to a human value of 1.71 µg.h/mL with a dose of 400 mg bd; the corresponding value for SR35021 was 1.50 µg.h/mL, \$ separate pharmacokinetic study † male>female, †† male<female, - = not measurable/calculable

Although combined values are tabulated above, sex differences were observed in some studies, mainly for the metabolite SR35021 and notably in mice in which male values were greater than those for females. There were no data for the rat reproductive toxicity studies, or for the HD of 100 mg/kg/day used in the fertility and early embryonic development and embryofetal development studies, although the pre/post-natal study HD of 50 mg/kg/day would be expected to have achieved an exposure ratio (ER) of about 2 for dronedarone based on the female Week 5 area under the plasma concentration time curve (AUC) value in the 26 week toxicity study.

Dronedarone was extensively metabolised in mice, rats, rabbits and dogs, both quantitatively and in terms of the range of metabolites generated, as in humans. The primary human plasma metabolites were the N-debutylated derivative SR35021 and the O-propanoic acid derivative SR90154 (respectively present at about the same or double the concentration of parent drug). SR35021, which was shown to be pharmacologically active (see *Primary pharmacology*), was generated in all experimental species, but systemic exposures, based on area under the plasma concentration time curve from zero time to 24 hours (AUC<sub>0-24 h</sub>) values relative to parent drug were variable. Exposures were comparable in mice, lower in rats and to a lesser extent rabbits, and considerably lower in dogs, with the rat and dog results being associated with higher levels of hydroxylated-SR35021 in the faeces (the major excretion route). Consequently, adequate plasma ERs for SR35021 were achieved only in mice and rabbits (7-20 with the HD). However, ERs based on the

combined AUC of dronedarone and SR35021, taking into account the potency difference (SR35021 is 2-10 fold less potent than the parent drug) are only slightly different from those based on the AUC of the parent drug alone. Therefore, exposure ratios based on the parent drug are used in the safety assessment.

Metabolite SR90154 was not routinely measured in the toxicity studies, but multiple-dosing pharmacokinetic studies indicated that this was present in mouse, rat and particularly dog plasma, in which 2 hour concentrations were in excess of those for the parent drug. In addition to dogs, systemic exposure to SR90154 was adequate in mice, in which it was present at a slightly lower concentration than parent drug at this sample time. There were no quantitative data in the corresponding rat study. However, a single-dose study in this species (MET0138) with multiple sampling showed that SR90154 concentrations after oral (PO) administration were in excess of those for the parent drug (for example respectively about 60% and 15% of 3 h radioactivity).

Excretion was primarily via the faeces in the experimental species, as in humans, and biliary excretion and enterohepatic recirculation were shown in rats, with many additional hydroxylated metabolites being identified in excreta as well as plasma. Based on the clinical summary, human plasma metabolites were present in mice, rats and dogs (rats sometimes excluded) or were relatively minor components (1.1-3.3% of radioactivity). Although hydroxy-SR90154 was a substantial rabbit plasma component it was otherwise seen only in rat bile and dog urine and faeces.

Overall, the species used for the toxicity studies were appropriate, with low oral bioavailability apparently reflecting first-pass metabolism rather than low absorption, as judged by urinary radioactivity recovery after oral compared with IV administration.

## Toxicology

Some species specificity was apparent in the oral repeat-dose toxicity studies and as tabulated above drug exposures in rats were relatively low. Mortality and body weight data indicate that the HD used in the carcinogenicity study (70 mg/kg/day) was probably the maximum tolerated dose, with a substantial impairment of body weight gain in males being seen (by 15%). Marked toxicity was noted in a short (2 weeks) study with a HD of 160 mg/kg/day eliciting a drug exposure ratio of about 15, as shown by mortalities and body weight losses.

Drug-related findings in the longest duration rat study included increased lung foamy cells and mesenteric lymph node (MLN) macrophages, thyroid columnar epithelium (with slightly lower serum T3) and slightly elevated plasma creatinine. The lung and MLN findings, also seen in the 13 week toxicity and 104 week carcinogenicity studies at all doses, as well as occasionally in mice and dogs, were manifestations of phospholipidosis, a phenomenon seen with many registered drugs including amiodarone. This appeared to be more pronounced in amiodarone toxicity studies, with dogs as well as rats being affected (Mazue, 1985), and amiodarone elicited increased liver and lung phospholipid content in a 2 week safety pharmacology study, a change not seen with dronedarone, suggesting dronedarone is less potent than amiodarone in the induction of phospholipidosis.<sup>3</sup> It is noteworthy, however, that foamy macrophages were widely distributed with the HD in the 2 week rat toxicity study, with other lymph nodes and the thymus, spleen, intestines and liver also being affected. Similar findings in humans have been implicated in clinical adverse reactions to amiodarone (Hruban, 1984).<sup>4</sup>

Creatinine is of some importance because of slight (10-15%) elevations seen in humans, which was shown to be associated with reduced tubular secretion (sponsor's *Clinical Overview*). In

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<sup>3</sup> Mazue, G. Summary dossier of toxicology studies conducted with amiodarone, 1985.

<sup>4</sup> Hruban, Z. Pulmonary and generalised lysosomal storage induced by amphiphilic drugs. *Environ Health Perspectives* 1984; 55: 53-76.

accordance with this, there was no histological evidence of renal toxicity in the rat (including the 13 week study in which creatinine was also slightly elevated) or dog toxicity studies despite slight increases in plasma creatinine and/or electrolytes. Proximal tubular vacuolation was seen in a 2 week mouse study, but only at lethal doses, and the drug ER at the NOEL (450 mg/kg/day) for this finding was about 10.

Minor effects of dronedarone on thyroid and related hormones were observed, and the effects differ from those of amiodarone probably due to the absence of iodine substituents in the dronedarone molecule. Slightly reduced serum T3 was noted in the 13 week rat study and in dogs (13 and 52 week studies), but it was only associated with thyroid histological findings in the former species (increased follicular columnar cells). Decreased plasma T3 and T4 were also reported in rats treated with dronedarone at 100 mg/kg/day for 2 weeks in a published study (van Beeren *et al.*, 2003), although plasma T3 was unaltered and T4 was significantly reduced in a 2-week safety pharmacology study in rats at up to 141 mg/kg/day in contrast to amiodarone which elicited reduced T3 and elevated rT3.<sup>5</sup> The basis for the decrease in T3 and/or T4 in rats treated with dronedarone may be the reported inhibition of T3 binding to the thyroid hormone receptors  $\alpha_1$  (TR $\alpha_1$ ) by the debutylated metabolite SR35021, and to a lesser extent to TR $\beta_1$ , with respective  $K_i$  values of 59 and 280  $\mu$ M (van Beeren *et al.*, 2003). Dronedarone itself showed little (TR $\alpha_1$ ) or no (TR $\beta_1$ ) inhibition of T3 binding. In the study by van Beeren *et al.* (2003) where plasma thyroid stimulating hormone (TSH) was measured, a significant increase in TSH, as well as rT3, occurred in rats treated with amiodarone (100 mg/kg/day), while plasma TSH was slightly decreased and rT3 unchanged in dronedarone-treated animals. The amiodarone-induced increase in serum TSH was associated with increased thyroid follicular cell tumours in a long-term carcinogenicity study (Mazue, 1985). TSH was not elevated in the dronedarone rat toxicity studies in which it was measured together with T3, T4 and prolactin, and no thyroid tumours were observed in long term carcinogenicity studies in mice and rats (see *Genotoxicity and carcinogenicity*). There were apparently no effects of treatment on serum T3, T4 and TSH in the dronedarone clinical trials (sponsor's *Clinical Overview*).

Besides MLN findings (see *Genotoxicity and carcinogenicity*), longer and higher exposure in the rat carcinogenicity study was associated with high incidences of oesophageal hyperkeratosis (also seen in the 2 week toxicity study) and testicular atrophy. The latter was not observed in any other toxicity studies and was possibly a potentiation of an age-related change (11-27% incidence in 2 control groups) or hormonal effects. Additional findings in the 2 week study were mainly seen with the substantially higher HD (and drug exposure), which was a lethal dose, and included increased adrenal weights, GI-tract changes (small intestinal/stomach distension, stomach erosion), female reproductive changes (increased dioestrus) and liver necrosis. The latter was not pronounced, and hepatotoxicity was not a feature of the oral dronedarone toxicity studies, with infrequent liver findings generally being seen only at lethal doses (for example hepatocellular vacuolation/apoptosis in the mouse 2 week study). Increased serum aspartate aminotransferases (AST) and alanine aminotransferase (ALT) were noted in a single HD female in the 13 week dog study, while mean ALT was slightly increased in HD females in the 52 week study in this species, but light and electron microscopic examinations failed to reveal any changes.

Compared with the rat studies, there were few effects of treatment in dogs, even though HD drug exposures were much higher, including a lack of foamy macrophage accumulation or mesenteric lymph node changes, other than at a HD achieving a very high drug exposure in the 2 week study (ER value of about 50). Although HD drug exposures in the 13 and 52 week studies were relatively high, this was not the case for the MD (ER of around 1.5) or the LD (ER not calculable). This less than ideal spacing of drug exposures precluded proper determination of safety margins for the

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<sup>5</sup> van Beeren, H.C. *et al.* Dronedarone acts as a selective inhibitor of 3,5,3'-triiodothyronine binding to thyroid hormone receptor- $\alpha_1$ : *in vitro* and *in vivo* evidence. *Endocrinology* 2003; 144: 552-558.

observed reductions in serum T3, and additionally, the HD in both of these studies resulted in decreased food consumption and body weight losses. Findings in the 2 week study at drug ER of about 28-50 included chronic inflammatory cell infiltration of the bile duct epithelium and stomach mucosa and green large intestinal contents, although these were not noted in the longer duration studies.

Overall, there were no findings in the oral toxicity studies which would preclude approval of registration, with a higher drug exposure in the rat carcinogenicity study compensating to a certain extent for the relatively low exposures in the shorter duration toxicity studies.

Dronedarone was originally developed for IV as well as oral use, but this was not pursued because of poor local IV tolerance in humans, and short-term studies with this route were conducted in rats, macaque (cynomolgus monkey) and dogs. IV administration was often poorly tolerated in the experimental species, although this depended on factors such as vehicle, site of cannula placement and injection or infusion dosing. Infusion site and liver abscesses were seen in the 4 week rat study using 60 min infusion into the femoral vein and a mannitol/monosodic phosphate vehicle (2-8 mg/kg/day), together with numerous associated findings, for example neutrophilia and anaemia. By contrast, there were relatively no effects of treatment in the corresponding dog study using the same vehicle but with a 60 minute infusion into the vena cava (1-4 mg/kg/day), although this resulted in infusion site and adjacent heart masses even with a saline control. End-of-infusion concentrations were higher in the dog study (80-420 ng/mL vs 17-130 ng/mL in the rat study), but dog exposures based on AUC<sub>0-24 h</sub> were low (ER values <1). It is noteworthy that an IV study was also conducted in macaques (cynomolgus monkey), in which it was poorly tolerated under the conditions used (injection dosing, 15% macrogol 400 vehicle), although this species was not used for PO studies.

### **Genotoxicity and carcinogenicity**

Dronedarone was not genotoxic in most adequately conducted genotoxicity assays (bacterial gene mutation, DNA repair *in vitro*, and chromosome aberration *in vitro* and *in vivo*), although concentrations that could be tested *in vitro* were severely limited by bacterial and mammalian cell toxicity. Slightly (relative to positive controls) increased mutation frequencies were seen in a V79 Chinese hamster forward mutation assay (*hgpert* locus) with and without metabolic activation, although there was no clear dose-response in the main study (5-10 µg/mL -S9, 10-25 µg/mL +S9), and values were said to be within historical control ranges (not provided in the study report). Negative results were obtained in a rat hepatocytic DNA repair assay and a chromosomal aberration assay in human peripheral blood lymphocytes. The dose used in the *in vivo* mouse micronucleus test was high (2000 mg/kg), and while the only single-dose toxicokinetic data was for a much lower dose (75 mg/kg), it would have achieved a drug systemic exposure well in excess of the human value. The weight of evidence based on all the genotoxicity assays suggests dronedarone is unlikely to pose a genotoxic risk in patients.

In contrast to the lack of genotoxicity, there were some positive findings in the long-term rodent carcinogenicity studies, presumably elicited by epigenetic mechanisms, as summarised in the following table. Significant increases were seen only with the HD (300 mg/kg/day in mice and 70 mg/kg/day in rats), and results were considered by an external scientific advisory panel (SAP, convened by the sponsor), with re-examination of relevant histological slides (Table 2).

Table 2: Findings from carcinogenicity studies

Tumour	Sex	Incidences <sup>&amp;</sup> and significance	
		Mouse	Rat
Mesenteric lymph node haemangioma	male		40% vs 7.2% (p<0.001)
	female	3.3% vs 0% (p=0.032) <sup>#</sup>	8.6% vs 2.9% (p=0.043)
Mesenteric lymph node hemangiosarcoma	female	3.3% vs 0% (p=0.032) <sup>#</sup>	
Mammary gland adenocarcinoma	female	17.9%*vs 3% (p<0.001)	
Histiocytic sarcoma	male	8.3% vs 0.8% (p=0.004)	
	female	11.7% vs 5.8%	
Harderian gland adenoma	female	11.7% vs 3.3% (p=0.024)	

<sup>&</sup> HD vs pooled controls, \* 21.4% in combination with mammary adenoacanthomas, <sup>#</sup> original report

### *Mesenteric lymph node tumours*

Haemangiomas and haemangiosarcomas in HD female mice were each reduced to single cases after SAP re-examination which would not be biologically or statistically significant. Haemangiomas in HD rats were, however, prominently increased in males and to a lesser extent females, associated with several other findings, and dronedarone and/or its metabolites were shown in a tissue distribution study to be present in mesenteric lymph nodes at high concentrations (relative to plasma) after PO administration. Although the pathogenesis of this tumour is not clear, associated changes such as angiectasis and sinusoidal erythrocytes/erythrophagocytosis and ectasia suggest a local change in blood flow, possibly related to the accumulation of foamy macrophages. Reactive proliferative changes (vascular sinus transformation as seen in humans) can be induced experimentally in rabbits by vascular or lymphatic occlusion (Steinmann *et al.*, 1982), and the SAP considered this to resemble angiomatous hyperplasia seen in the rat study.<sup>6</sup>

### *Mammary gland adenocarcinomas*

These showed a prominent increase in mice, alone or in combination with adenoacanthomas, and were probably related to slight increases in prolactin demonstrated with 300 mg/kg in mechanistic studies. Although incidences of these tumours were not elevated in rats, and prolactin was unaffected in the rat studies in which it was measured (13 and 26 week toxicity studies), doses and drug exposures were lower. Nevertheless, drug exposures at the NOEL for mammary gland tumour development were in excess of the human value (ER of 3 for mice and 5 for rats). Prolactin was apparently not monitored in the dronedarone clinical trials, but several registered drugs are known to elicit elevations, including metoclopramide, chlorpromazine and haloperidol, with the latter also increasing female mouse mammary tumours.

### *Histiocytic sarcomas and Harderian gland adenomas*

Histiocytic sarcoma incidences were increased in mice, although the increase in female mice was not statistically significant. The HD male incidence of 8.3% was within a historical control range of 0-13.3% quoted by the SAP. These data, however, referred to 18 independent studies conducted at other laboratories. No increase was observed in rats. The biological significance of the HD increase only in one species, and its relevance to humans, is not clear, especially as the human counterpart is very rare. Harderian gland adenomas were unaffected in male mice, in which the control incidence was high (20.8%), or in rats, and the relevance of the HD female increase was

<sup>6</sup> Steinmann, G. et al. Morphological findings in lymph nodes after occlusion of their efferent lymphatic vessels and veins. Lab Invest 1982; 47: 43-50.

also uncertain, especially given the absence of this gland in humans. Most likely, this represents a false positive reflecting statistical significance being set at  $p < 0.05$  for a common tumour. The female control incidence was 3.3%, and a cut off of  $p < 0.005$  or  $P < 0.01$  would be more appropriate.

Overall, although dronedarone genotoxicity was not demonstrable in most genotoxicity studies, tumourigenic responses were observed in the mesenteric lymph nodes, Harderian gland, haemolymphoreticular system and mammary glands. The relevance of these findings to humans is uncertain. The findings should not preclude approval of the drug based on sex and species distribution, drug exposures at which they occurred and the nature of the tumours.

### **Reproductive toxicity**

Dronedarone was teratogenic in rats. Multiple fetal malformations were seen in the main study at 100 mg/kg/day and in a dose range-finding study at 80 and 160 mg/kg/day. The 100 mg/kg/day dose was associated with impaired maternal body weight gain, increased post-implantation loss and reduced fetal weight. There were no supporting toxicokinetic data, and accurate dose-adjustment using available data was precluded by greater than dose-proportionality for AUC<sub>0-24 h</sub> values. Expected drug exposures would be low based on data from a 2 week toxicity study, that is, ER value of only 0.5 at the No Observable Effect Level (NOEL) of 30 mg/kg/day, and  $>2$  with the 100 mg/kg/day dose. The ER at 80 mg/kg/day based on AUC at 70 mg/kg/day in the 2 week repeat dose study was slightly higher than 2 times the clinical AUC. Although there were no such findings in the corresponding rabbit study, there was an inadequate number of litters available for examination at the maternotoxic HD (200 mg/kg/day), and drug exposures with the low dose (LD) and mid-dose (MD) were very low (ER values of  $\leq 0.3$  based on the gestation day (GD) 18 AUC<sub>0-24 h</sub> value). However, the presence of a single malformed dead fetus in a pilot study after treatment with the same HD suggests that dronedarone may also exhibit teratogenicity in this species, although this could be an incidental finding. In contrast to rats, placental transfer of radioactivity was not measurable in rabbit fetuses after PO administration of [<sup>14</sup>C]dronedarone, although radioactivity was detected in fetal gastrointestinal contents. By comparison with dronedarone, amiodarone was not shown to be teratogenic (Mazue, 1985; Cordarone X product information).

Fertility was not statistically significantly affected by PO doses of 10-100 mg/kg/day, but there were tendencies for longer/irregular oestrus cycles at the MD and HD and non-pregnancies in 2/22 HD rats, which were probably treatment-related. The HD resulted in reduced implantations and increased resorptions, with an associated lower number of live fetuses. As noted above, an exact estimate of drug exposure with this HD is difficult, but it was low at 30 mg/kg/day (ER value of only 0.5). In the pre- and post-natal study, a HD of 50 mg/kg/day affected maternal body weight gains (reduced during gestation, increased during lactation), and although pup weight gains over post-partum days 1-4 were slightly lower, subsequent development of offspring was unaffected by maternal treatment. Maternal drug exposures were low (ER value of about 2 with the HD, based on the week 5 AUC value of females in the 26-week repeat dose toxicity study), although substantial milk secretion of radioactivity was shown in a pharmacokinetic study after single PO treatment (milk/plasma ratios of 2.3-4.6 at 2-4 hours). Additionally, the dose used in this study (30 mg/kg) resulted in a high radioactivity concentration in the gastric contents of suckling pups (3.5 µg eq/g at the last sample time of 24 hours).

### **Local tolerance**

As noted above (*General toxicity*), IV tolerance of 1-2 mg/mL solutions was generally poor in repeat-dosing studies, which was not the case in single-dose studies in rabbits, although intra-arterial and perivenous injections resulted in moderate reactions. These studies, together with those investigating *in vitro* haemolysis, were probably to support the original intention of IV administration. Haemolysis of human blood was minimal using concentrations of up to 0.8 mg/mL blood and hydroxypropyl β-cyclodextrin/glucose vehicle/diluent.

## Impurities

The N-debutyl derivative SR35021 is the only specified impurity (limit of 0.2%), and this is a substantial metabolite in all the experimental species examined and so does not need to be qualified. According to the nonclinical overview, impurity SR194090 showed a genotoxic structural alert and was present in batches at 4-67 ppm, which was above the concentration limit at the threshold of toxicological concern of 1.5 µg/day. This compound was tested in adequate bacterial reverse gene mutation and mouse lymphoma forward mutation (*tk* locus) assays with negative results.

## Nonclinical Summary and Conclusions

*In vitro* and *in vivo* studies indicated that dronedarone acted as a cardiac ion channel blocker with demonstrable antiarrhythmic activity, and was similar to but not identical to amiodarone. Toxicity studies were adequate, although daily dosing resulted in lower than ideal drug exposures in rats, with no findings that would preclude approval of registration. As in the clinical trials, some studies showed slight increases in serum creatinine, but there were no indications of nephrotoxicity by histological examination.

The long-term carcinogenicity studies showed an increased incidence of mammary gland adenocarcinomas in female mice, most likely resulting from slightly elevated prolactin which was shown to be elicited by treatment in other studies. Dronedarone is similar to some other registered drugs in this respect (for example haloperidol). Other tumourigenic findings appeared to be of little relevance to humans, although it would be difficult to exclude this completely.

Dronedarone was teratogenic in rats, and should not be used by pregnant women. A demonstrated excretion of parent drug and/or metabolites in rat milk should also preclude use during breastfeeding.

*Issues likely to be addressable from the clinical data*

Dronedarone elicited small elevations in prolactin in female mice, even following single administration, although this was not demonstrated in rats and it was not measured in dogs. Irregular oestrous cycles and testicular atrophy observed in rats also suggested potential hormonal effects. Prolactin appears not to have been measured in the clinical trials, and it may be prudent to investigate this and other related hormones in order to define the activity of dronedarone more completely.

## IV. Clinical Findings

### Introduction

The data included in the submission represent a clinical development program for dronedarone, a new chemical entity and an antiarrhythmic agent. The data represent extensive Phase I and Phase II development, but the Phase III data consist primarily of placebo controlled trials. Limited comparator controlled data were contained within the submission. The sponsor requested a Priority Review.

A total of 54 clinical studies, conducted in 8236 subjects, 4867 of whom were treated with dronedarone, were included in the development program.

There were six studies submitted in support of pharmacodynamics. In these studies there were 223 subjects, 162 treated with dronedarone and eleven with amiodarone.

**Study PDY5487**, 12 healthy volunteers, all treated with dronedarone.

**Study PDY5923**, 31 healthy volunteers, 21 treated with dronedarone.

**Study PDY2399**, 21 patients, 14 treated with dronedarone, seven with amiodarone.



**Study PDY2400.** 23 patients with impaired left ventricular function (LVF), all treated with dronedarone.

**Study ACT2401,** 124 patients with impaired LVF, 84 treated with dronedarone.

**Study PDY2402,** twelve subjects, eight treated with dronedarone and four treated with amiodarone.

There were three studies of bioavailability conducted in 33 subjects, all of whom were treated with dronedarone:

**Study 2397,** 12 healthy male volunteers, all received dronedarone.

**Study ALI3179,** 12 healthy male volunteers, all treated with dronedarone.

**Study ALI3180,** 9 healthy male volunteers, all treated with dronedarone.

There were four formulation development/bioequivalence studies conducted in 84 healthy male volunteers, all of whom were treated with dronedarone:

**Study BDR2889,** 29 healthy male volunteers, all treated with dronedarone.

**Study GAR3144,** 19 healthy male volunteers all treated with dronedarone.

**Study GAR3585,** 24 healthy male volunteers, all treated with dronedarone.

**Study BDR4680,** 12 healthy male volunteers, all treated with dronedarone.

There were 32 studies of dronedarone pharmacokinetics conducted in 844 subjects, 779 of whom were exposed to dronedarone:

**Study TDU2163,** 48 volunteers, 36 treated with dronedarone.

**Study TDU2164,** 28 volunteers, 21 treated with dronedarone.

**Study BEX2770,** 12 volunteers, all treated with dronedarone.

**Study TDU3007,** 32 volunteers, 24 treated with dronedarone.

**Study TDU4899,** 40 volunteers, 30 treated with dronedarone.

**Study TDR2395,** 52 volunteers, 52 treated with dronedarone.

**Study LIN2890,** 21 volunteers, 21 treated with dronedarone.

**Study TDR3549,** 41 volunteers, 41 treated with dronedarone.

**Study TDR2394,** 42 subjects with benign ventricular arrhythmia, all treated with dronedarone.

**Study POP2769,** 54 healthy young and elderly volunteers, all treated with dronedarone.

**Study POP2896,** 3 subjects, all exposed to dronedarone.

**Study POP5820,** 26 subjects, all treated with dronedarone.

**Study PDY5850,** 33 elderly males, 21 treated with dronedarone.

**Study INT2631,** 14 volunteers, all treated with dronedarone.

**Study INT2634,** 13 volunteers, all treated with dronedarone.

**Study INT2636,** 19 volunteers, all treated with dronedarone.

**Study INT2931,** 8 volunteers, 5 treated with dronedarone.

**Study INT3353,** 17 volunteers, all treated with dronedarone.

**Study INT3560,** 18 volunteers, all treated with dronedarone.

**Study INT3561,** 12 volunteers, all treated with dronedarone.

**Study INT3683**, 12 volunteers, all treated with dronedarone.

**Study PDY3828**, 49 volunteers, 36 treated with dronedarone.

**Study INT4074**, 30 volunteers, all treated with dronedarone.

**Study INT4442**, 16 volunteers, all treated with dronedarone.

**Study INT4695**, 21 volunteers, all treated with dronedarone.

**Study INT4880**, 24 volunteers, all treated with dronedarone.

**Study INT4881**, 28 volunteers, all treated with dronedarone.

**Study INT4882**, 19 volunteers, all treated with dronedarone.

**Study INT4884**, 29 volunteers, all treated with dronedarone.

**Study INT4886**, 24 volunteers, all treated with dronedarone.

**Study INT5084**, 39 volunteers, all treated with dronedarone.

**Study INT5139**, 20 volunteers, all treated with dronedarone.

In addition there were two population pharmacokinetic studies: **Study POH0203** and **Study POH0204**; and one pooled analysis: **Study PMH0057**.

There were seven studies, conducted in 6352 patients, 3445 treated with dronedarone, submitted in support of efficacy:

**Study DRI3550 DAFNE**, 270 patients, 204 treated with dronedarone.

**Study EFC4508 ERATO**, 174 patients, 85 treated with dronedarone.

**Study EFC3153 EURIDIS**, 612 patients, 411 treated with dronedarone.

**Study EFC4788 ADONIS**, 625 patients, 417 treated with dronedarone.

**Study EFC5555 ATHENA**, 4604 patients, 2291 treated with dronedarone.

There were two studies for a different route than that applied for under the present application:

**Study ACT2771**, 61 patients, 31 treated with dronedarone.

**Study PDY2945**, 6 subjects, all treated with dronedarone.

There were a further two studies, conducted in 700 patients, 364 treated with dronedarone, that were evaluable only for safety:

**Study DRI3151/ Study LTS3841**, 73 patients, 54 treated with dronedarone.

**Study EFC4966 ANDROMEDA**, 627 patients, 310 treated with dronedarone.

All the clinical studies appear to have been conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki.

There were also supplementary clinical data and reports submitted in response to the clinical evaluation report. The data included the study report for **Study Efc4968 DIONYSOS** and a written response to issues raised in the clinical evaluation report. **Study Efc4968 DIONYSOS** provided data in support of efficacy and safety for dronedarone in comparison with amiodarone. **Study Efc4968 DIONYSOS** was conducted in 504 subjects, 249 of whom were exposed to dronedarone. There were no additional pharmacokinetic, pharmacodynamic or post-marketing data included in the supplementary data.

## Pharmacokinetics

### Bioavailability Study Reports

**Study 2397** was a single centre, randomised, open label, 3 treatment period (with the first two treatment periods being a 2x2 crossover design) bioavailability study. The study was conducted in 12 healthy Caucasian male volunteers aged 18 to 40 years. The study treatments were:

- Dronedarone 100 mg capsules, 800 mg administered orally, fed
- Dronedarone 100 mg capsules, 800 mg administered orally, fasted
- 1 mg/mL ampoules, 60 mg administered intravenously

Food increased exposure to dronedarone by seven fold. Absolute bioavailability was 15% under fed conditions.

**Study ALI3179** was a single centre, open-label, randomised 3 period crossover study of the effect of fat content on bioavailability compared to fasted conditions. The study included nine healthy male volunteers aged 21 to 38 years. The study treatment was dronedarone 400 mg tablets containing a surfactant (pluronic F127, also known as poloxamer 407) administered as:

- 800 mg orally, fasted
- 800 mg orally immediately after a low fat meal
- 800 mg orally immediately after a fat rich meal

Each treatment was a single dose with a 7 day washout period between doses. The bioavailability of dronedarone was increased in the fed state, and more so by a fat-rich meal.

**Study ALI3180** was a single centre, open-label, randomised, 3 period crossover study of the effect of the fat content of a meal, in comparison with fasted conditions, on the bioavailability of dronedarone. The study included nine healthy male volunteers aged 24 to 39 years. The study treatment was dronedarone 400 mg tablets containing pluronic F127 (poloxamer 407) administered as:

- 800 mg orally, fasted
- 800 mg orally immediately after a low fat meal
- 800 mg orally immediately after a fat rich meal

Dronedarone bioavailability was increased in the fed state, and increased slightly more by a fat rich meal.

#### *Evaluator's comments:*

Absolute bioavailability of dronedarone is 15% under fed conditions (Study 2397). Food increases exposure to dronedarone by seven fold (Study 2397, Study ALI3179). A fat rich meal further increases the bioavailability of dronedarone (Study ALI3179).

### Comparative bioavailability and bioequivalence study reports

**Study BDR2889** was a single centre, open label, crossover, two parallel group, relative bioavailability study of three different tablet formulations of dronedarone in comparison to a standard capsule conducted under fasted and fed conditions. One group was studied in the fasted state and the other in the fed state. The study included 29 healthy male volunteers aged 19 to 33 years. There were 13 subjects in the fasted group, and 16 in the fed group. The study treatments were:

- Dronedarone 400 mg simplex (standard) tablets
- Dronedarone 400 mg tablets containing 2 differing concentrations of pluronic F127 (poloxamer 407)
- Dronedarone standard capsule 200 mg

The treatments were administered as a single 800 mg doses, administered orally, and separated by a 7 day washout period. Five subjects withdrew prematurely (one due to an AE: dizziness), and 24 subjects completed the study. The tablets containing pluronic F127 (poloxamer 407) improved bioavailability in the fasted state but did not significantly improve bioavailability in the fed state.

**Study GAR3144** was a single centre, open label, crossover, two parallel group relative bioavailability study of three capsule formulations in comparison with a standard capsule, under fasted and fed conditions. One group was studied under fasted conditions and the other under fed conditions. The study included 19 healthy male volunteers aged 20 to 32 years - eight subjects in the fasted group and eleven in the fed group. The study treatments were: dronedarone 200 mg capsules: three different formulations containing the lipid excipient Gelucire in comparison with standard capsule. Three subjects discontinued - one because of an AE (upper respiratory tract infection). Sixteen subjects completed: eight in each group. The Gelucire formulations increased bioavailability, particularly Formulation 2, and particularly in the fasted state.

**Study GAR3585** was a single centre, open label, crossover, two parallel group relative bioavailability study of three different tablets presenting different in vitro dissolution profiles in comparison to a reference tablet under fed and fasted conditions. One group was studied in the fasted state and the other in the fed. There were 24 healthy male volunteers aged 19 to 40 years included in the study. There were 12 subjects in the fasted group and 12 in the fed. The study treatments were dronedarone 400 mg tablets:

- Reference
- Fast dissolution profile
- Medium dissolution profile
- Slow dissolution profile

The treatments were administered as a single 800 mg dose, administered orally. The four single doses were separated by a 7 day washout period. All subjects completed the study. In fasted conditions, the new formulations had lower bioavailability than the standard. Under fed conditions, the fast dissolution formulation had the highest bioavailability.

**Study BDR4680** was a single centre, open label, randomised, two period, crossover relative bioavailability study between the oval shaped Phase III tablet and the round shaped Phase II tablet. An internal marker,  $^{13}\text{C}$ -dronedarone was co-administered as a capsule with each of the tablets. Twelve healthy male volunteers aged 19 to 34 years were included in the study. The study treatments were:

- Phase III 400 mg tablets and 100mg  $^{13}\text{C}$ -dronedarone capsules
- Phase II 200 mg tablets and 100mg  $^{13}\text{C}$ -dronedarone capsules

The treatments were administered in fasted conditions, as a single 800 mg, with a 7 day washout period between the two doses. All subjects completed the study.  $C_{\text{max}}$  was 22% higher with the Phase III formulation but AUC,  $t_{\text{max}}$  and  $t_{1/2}$  indicated bioequivalence. The Phase III formulation used in Study BDR4680 is identical to that proposed for marketing in Australia.

### *Evaluator's comment*

Bioequivalence was demonstrated between the Phase II and Phase III formulations of dronedarone. The studies investigated different formulations containing pluronic F127 (poloxamer 407), Gelucire (a lipid excipient) and standard formulations. The formulation intended for marketing contains poloxamer 407 but does not appear to contain Gelucire.

### ***In Vitro Studies Supporting Pharmacokinetics***

**Study LPH0006:** was an *in vitro* characterisation of the binding of  $^{14}\text{C}$ -dronedarone to human plasma proteins. Dronedarone was found to be extensively protein bound (99.7%) and binding was non-saturable at concentrations up to 50,000 ng/mL. Binding to purified serum albumin and  $\alpha$ 1-acid glycoprotein was 98.4 to 98.9% and 77.6 to 88.6% respectively, and also non-saturable.

**Study LPH0021** was an *in vitro* characterisation of the binding of  $^{14}\text{C}$ -SR35021 (the major metabolite of dronedarone) to human plasma proteins.  $^{14}\text{C}$ -SR35021 was extensively protein bound (98.5%) and binding was not saturable at concentrations up to 50,000 ng/mL. Binding to purified serum albumin was 94.5 to 95.3% and not saturable. Binding to  $\alpha$ 1-acid glycoprotein was concentration dependent, ranging from 73.4% at 25 ng/mL to 29.8% at 50,000 ng/mL.

**Study MIH0006** was an *in vitro* study of the potential for co-administered drugs to inhibit the *N*-debutylation of dronedarone using human liver microsomes. The study examined captopril, digoxin, diltiazem, lidocaine, nifedipine, propranolol, quinidine, ticlopidine, verapamil and warfarin. The study used microsomes from three human livers and used ketoconazole as a positive control. Captopril, digoxin, lidocaine, propranolol and warfarin were not strong inhibitors of *N*-debutylation of dronedarone. Diltiazem, nifedipine, ticlopidine, verapamil and quinidine inhibited the *N*-debutylation of dronedarone by more than 30% and ketoconazole almost completely blocked the *N*-debutylation of dronedarone. However, the investigators concluded that at normally observed plasma concentrations, clinically significant interactions would be probable only with ticlopidine and quinidine.

**Study MIH0007** was an *in-vitro* study of the potential for dronedarone or amiodarone to inhibit cytochrome P450 (CYP) enzymes using human liver microsomes. The following substrates and controls were used:

Substrate	CYP	Investigated reaction	Inhibitor
Phenacetin	1A2	0-deethylation	Furafylline
Coumarin	2A6	7-hydroxylation	Pilocarpine
Bufuralol	2D6	1'-hydroxylation	Quinidine
Chlorzoxazone	2E1	6-hydroxylation	Diethyl thithiocarbamate
Tolbutamide	2C9	methylhydroxylation	Sulfaphenazole
Mephenytoin	2C19	4'-hydroxylation	Papaverine
Nifedipine	3A4	Oxidation	Ketoconazole

Dronedarone did not significantly inhibit CYP1A2, CYP2C9, CYP2C19 or CYP2E1. However, CYP2D6 was inhibited by 3.8%, and CYP3A4 by 0.5% at expected plasma concentrations of dronedarone (0.2  $\mu\text{M}$ ).

**Study MIH0037** was an *in vitro* study that investigated the potential for SR35021 (the primary metabolite of dronedarone) to inhibit CYP enzymes using human liver microsomes. The study used the following substrates and controls:

Substrate	CYP	Investigated reaction	Inhibitor
Phenacetin	1A2	O-deethylation	Furafylline
Coumarin	2A6	7-hydroxylation	Pilocarpine
Tolbutamide	2C9	methylhydroxylation	Sulfaphenazole
Mephenytoin	2C19	4'-hydroxylation	Tranylecypromine
Bufuralol	2D6	1'-hydroxylation	Quinidine
Chlorzoxazone	2E1	6-hydroxylation	Diethyldithiocarbamate
Nifedipine	3A4	oxidation	Ketoconazole

SR35021 inhibited all of the CYP enzymes studied: with a  $K_i$  for CYP1A2 of 30.6  $\mu\text{M}$ , CYP2A6 of 32.7  $\mu\text{M}$ , CYP2C9 of 18.3  $\mu\text{M}$ , CYP2C19 of 11.2  $\mu\text{M}$ , CYP2D6 of 4.37  $\mu\text{M}$ , CYP2E1 of 45.2  $\mu\text{M}$  and CYP3A4 of 8.12  $\mu\text{M}$ .

**Study MIH0138** was an *in vitro* study investigating the CYP isoforms involved in the oxidation of SR35021. The study used human liver microsomes, purified CYP isoforms from transfected insect cells (Supersomes) and cultured human hepatocytes. NADPH-dependent metabolism of SR35021 was not observed in human liver microsomes, but in Supersomes CYP2D6 and CYP3A metabolised SR35021. In human hepatocytes, CYP3A accounted for approximately 20% of SR35021 metabolism and CYP2D6 accounted for little SR35021 metabolism.

**Study MIH0441** was an *in vitro* study investigating the potential for dronedarone and SR35021 to inhibit CYP2B6 using human liver microsomes. Bupropion was used as the CYP2B6 substrate and mAb-2B6 was used as the positive control. The apparent  $K_i$  for the inhibition of CYP2B6 was 12.0  $\mu\text{M}$  for dronedarone and 56.9  $\mu\text{M}$  for SR35021.

**Study MIH0460** was an *in vitro* study investigating the potential for dronedarone and SR35021 to inhibit CYP2C8 using human liver microsomes. Paclitaxel was used as the CYP2C8 substrate and quercetin as the positive control. Dronedarone did not produce significant inhibition of CYP2C8 but the  $K_i$  for SR35021 was 36.6  $\mu\text{M}$ .

**Study MIV0144** was an *in vitro* study investigating the effect of dronedarone upon the expression of CYP 1A, 2A and 3A in primary cultures of human hepatocytes. The substrates used were 7-ethoxyresorufin (CYP1A1), phenacetin (CYP1A2), coumarin (CYP2A1) and nifedipine (CYP3A4). Controls used were dexamethasone,  $\beta$ -naphthoflavone and phenobarbital. Western blots using polyclonal antibodies against CYP1A2 and CYP3A4 were performed. No inducing or inhibiting effects for dronedarone were observed.

**Study MIV0158** was an *in vitro* study of dronedarone metabolism using human hepatic models: primary cultures of hepatocytes; and hepatic microsomal fractions. The models investigated the oxidative pathway and the glucuronidation pathway. The models were used to explore the stepwise biotransformation of dronedarone and its metabolites. LC-MS/MS analysis indicated the metabolic products of dronedarone and SR35021. Based on the results a metabolic pathway was proposed.

**Study MIV019** was an *in vitro* study of the main CYP isozymes involved in dronedarone metabolism using human liver microsomes. The study used hepatic microsomal preparations from rats treated with specific enzyme inducers ( $\beta$ -naphthoflavone for CYP1A2, Phenobarbital for CYP2B6 and CYP3A4 and dexamethasone for CYP3A4). Inhibitors of specific CYP isozymes (7-ethoxyresorufin for CYP1A1, 7-methoxycoumarin for CYP1A2, d-benzphetamine for CYP2B6, debrisoquine for CYP2D6 and nifedipine for CYP3A4) were also used to identify the CYP enzymes involved in dronedarone metabolism. The study concluded that CYP3A is the primary CYP family involved in the *N*-debutylation of dronedarone to SR35021.

**Study MIV0281** was an *in vitro* study of the role of CYP3A4 in the hepatic metabolic clearance of dronedarone using primary cultures of human hepatocytes. Dronedarone was rapidly and extensively metabolised, primarily to SR35021. SR35021 was subsequently metabolised by deamination to SR90154, and by *O*-dealkylation and hydroxylation. More than 84% of the hepatic metabolic clearance of dronedarone was due to CYP3A4 activity.

**Study AIV0062** was an *in vitro* study of transepithelial transport of dronedarone and the effect of dronedarone on the efflux transporters for vincristine and digoxin using Caco-2/TC-7 cell monolayers. Transport of dronedarone was measured in the apical to basal and also in the basal to apical directions in the presence and absence of quinidine. Dronedarone exhibited transepithelial transport with a “basal to apical”/“apical to basal” ratio of 2.5. Dronedarone inhibited the efflux of vincristine and digoxin with a similar potency to cyclosporine and a greater potency compared to verapamil and quinidine.

*Evaluator's comment:*

*In vitro* studies indicate that

- Dronedarone is 98.4 to 98.9% bound to serum albumin, 77.6 to 88.6% bound to  $\alpha$ 1-acid glycoprotein, and this protein binding is non-saturable (Study LPH0006).
- The major metabolite of dronedarone, SR35021, has non-saturable binding of 94.5 to 95.3% to serum albumin, but has saturable binding to  $\alpha$ 1-acid glycoprotein, ranging from 73.4% at 25 ng/mL to 29.8% at 50,000 ng/mL (Study LPH0021)
- In vitro, diltiazem, nifedipine, ticlopidine, verapamil and quinidine inhibited the N-debutylation of dronedarone by more than 30% and ketoconazole almost completely blocked the N-debutylation of dronedarone (Study MIH0006).
- Dronedarone did not significantly inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1, CYP2D6, CYP3A4 (Study MIH0007); CYP2B6 (Study MIH0441); or CYP2C8 (Study MIH0460)
- SR35021 is unlikely to have significant inhibition of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 (Study MIH0037); CYP2B6 (Study MIH0441); or CYP2C8 (Study MIH0460) at the plasma concentrations observed in clinical studies.
- CYP3A4 accounts for approximately 20% of SR35021 metabolism (Study MIH0441).
- Dronedarone did not induce CYP1A2 or CYP3A4 in vitro (Study MIV0144).
- CYP3A4 is the primary CYP family involved in the N-debutylation of dronedarone to SR35021 (Study MIV019).
- More than 84% of the hepatic metabolic clearance of dronedarone was due to CYP3A4 activity (Study MIV0281).
- Dronedarone exhibits transepithelial transport with a “basal to apical”/“apical to basal” ratio of 2.5; and in addition inhibits the efflux of vincristine and digoxin with a similar potency to cyclosporine and a greater potency compared to verapamil and quinidine (Study AIV0062)

### Human Pharmacokinetic Studies

**Study TDU2163** was a single centre, ascending dose, double blind, placebo controlled pharmacokinetics and tolerability study. The tolerability measures included ECG, QTc, Holter, vital signs and adverse effects (AEs). The study treatments were dronedarone 25 mg and 100 mg capsules. The treatments were: 25, 50, 100, 200, 400, 500, 600, 700, 800, 1000, 1200 or 1400 mg as a single dose. The comparator was placebo capsules. A total of 48 healthy males aged 20 to 39 years were included in the study. All 48 subjects completed the study. There were three subjects per study group (also one placebo treated subject per group). AUC and C<sub>max</sub> appeared to be dose proportional.

**Study TDU2164** was a single centre, ascending dose, double blind, placebo controlled pharmacokinetics and tolerability study (Phase 1). ECG and Holter recordings were performed with

the intent of studying the effect on QTc prolongation. The study treatment was dronedarone 1mg/mL mannitol solution. The study doses were 5, 10, 20, 40, 60, and 80 mg as intravenous infusions. The 5 to 40 mg doses were infused over 5 minutes and the 40 and 80 mg doses were infused over 60 minutes. The comparator was placebo infusion. The study included 28 healthy male volunteers aged 19 to 40 years. All 28 completed the study. There were three treated subjects and one placebo subject per dose level. The plasma dronedarone profiles indicate a redistribution phase (two-compartment model). There appeared to be dose proportionality for AUC and C<sub>max</sub>.

**Study BEX2770** was a single centre, open label, parallel group study of the pharmacokinetics, metabolism and tolerability of dronedarone. The study treatments were dronedarone 200 mg capsules (including <sup>13</sup>C labelled and <sup>14</sup>C labelled dronedarone, 800 mg orally, single dose; and dronedarone 0.33 mg/mL ampoules (including <sup>13</sup>C labelled and <sup>14</sup>C labelled dronedarone), 40 mg, administered as IV infusion over 60 min, single dose. The study included twelve healthy male volunteers aged 60 to 69 years. There were six subjects in the oral group and six in the IV group. Following the oral dose 5.8±1.2% of the dose was excreted in urine and 83.9±5.1% in faeces. Following the IV dose 8.3±1.9% of the dose was excreted in urine and 74.5±7.8% was excreted in faeces. Mass spectrographic analysis was performed on the identified metabolites and the metabolic pathways for dronedarone in humans were proposed.

**Study TDU3007** was a single centre, ascending dose, double blind, placebo controlled study of the local and general tolerability, effects on ECG and pharmacokinetics of intravenous dronedarone. The study treatment was dronedarone 4 mg/mL 10 mL cyclodextrine solution vials. The study doses were 10 mg (n=3), 20 mg (n=3), 40 mg (n=6), 60 mg (n=6) and 80 mg (n=6). The comparator treatment was placebo: 10 mL cyclodextrine vials (n=8). The study drug was administered as a single dose, intravenously over 30 minutes. The study included 32 healthy male volunteers aged 22 to 40 years. All 32 subjects completed the study. The pharmacokinetics of dronedarone and SR35021 were linear. There was an increase in QTc from baseline in the 20, 40 and 60 mg dose groups. Otherwise there were no significant changes in ECG or Holter readings.

**Study TDU4899** was a single centre, ascending dose, randomised, placebo controlled, double blind, two period crossover study of the pharmacokinetics of dronedarone in the fed and fasted states conducted in Japanese subjects. The study treatments were dronedarone 100 mg and 400 mg tablets. The study treatments were: 800 mg in the fed and fasted states (all study subjects) and dronedarone 100, 200, 400, 800, or 1200 mg or placebo. There were six subjects in each dose group and ten in the placebo group. Hence each subject received three single oral doses. The study included 40 healthy male Japanese volunteers aged 20 to 26 years. All 40 subjects completed the study. The pharmacokinetics of dronedarone were linear.

**Study TDR2395** was a single centre, ascending dose, double blind, randomised, placebo controlled, sequential group, single and multiple dose (under fed conditions) study of the pharmacokinetics, pharmacodynamics and tolerability of dronedarone. The study treatment was dronedarone 200 mg capsules. The study doses were: 400, 600 or 800 mg twice daily, or 800, 1200 or 1600 mg once daily. The treatment duration was for 14 days. The comparator was placebo. The study included 52 healthy male volunteers aged 21 to 39 years. Forty four subjects completed the study. There did not appear to be any autoinduction or autoinhibition of dronedarone elimination. There was no indication of accumulation of SR35021 with repeated dosing.

**Study LIN2890** was a single centre, randomised, open label, three treatment, three period crossover study of the dose proportionality of dronedarone pharmacokinetics after single and repeated (twice daily) dosing. The study treatment was dronedarone 100 and 400 mg tablets. The dosing regimens were: 200, 400, or 800 mg as a single dose on Day 1, followed by twice daily from Days 5 to 13 then once daily on Day 14. The repeat dosing treatment duration was 10 days. The study included 21 healthy male volunteers aged 19 to 40 years. All 21 subjects completed the study. There was a



greater than expected increased in  $C_{\max}$  and AUC with increasing dose. A two fold increase in dose led to a 2.8 (2.62 to 2.93) and 2.6 (2.46 and 2.73) increase in dronedarone and SR35021  $C_{\max}$  on Day 14; and a 3.1 (2.92 to 3.20) and 2.8 (2.71 to 2.93) increase in  $AUC_{0-12}$  respectively. From 200 mg to 800 mg the mean dronedarone  $t_{1/2}$  increased significantly from 9.8 to 19.6 hours at Day 1 and from 26.9 to 31.2 hours at Day 14 and increased significantly from Day 1 to Day 14. The mean SR35021 half-life ( $t_{1/2}$ ) increased significantly from 16.2 to 21.9 hours at Day 1 and decreased from 23.4 to 20.4 hours at Day 14.

**Study TDR3549** was a single centre, randomised, double blind, placebo controlled, five sequential group study of the safety, pharmacokinetics and pharmacodynamics of repeated ascending doses of dronedarone twice daily in fed conditions. The study treatment was dronedarone 200 mg capsules. The study included 41 healthy male volunteers aged 21 to 40 years. All 41 subjects completed the study. The dosing regimens were 800 mg (n=6), 1000 mg (n=6), 1200 mg (n=7), 1400 mg (n=6), and 1600 mg (n=6), all of which were administered orally, twice daily. The comparator was placebo (n=10). There was a greater than proportional increase in  $C_{\max}$  and AUC.

**Study TDR2394** was a single centre, double blind, placebo controlled, ascending dose, pharmacokinetics and tolerability study of dronedarone in patients with benign ventricular arrhythmia. ECG and Holter changes were also recorded during the study. The study drug was dronedarone 100 mg capsules administered at doses of 100, 200, 400, or 800 mg once daily for 20 days. Administration was orally after breakfast. The study included 42 patients with benign ventricular arrhythmia, 36 male, 6 female, with an age range of 18 to 62 years. Forty one subjects completed the study. At steady state,  $C_{\max}$  and AUC increased more than dose proportionally.

#### *Evaluator's comment*

Dose proportionality for oral dosing was demonstrated (Study TDU2163, Study TDU4899). Dose proportionality for intravenous dosing was demonstrated (Study TDU2164, Study TDU3007). The *in vivo* metabolism of dronedarone was investigated (BEX2270). Multiple dose studies were conflicting: there was some evidence of no autoinduction or inhibition of SR35021 production (Study TDR2395), but other evidence of  $t_{1/2}$ , AUC and  $C_{\max}$  increasing with repeat dose studies (Study LIN2890, Study TDR3549, Study TDR2394).

### **Pharmacokinetic Studies Examining Intrinsic Factors**

**Study POP2769** was a single centre, double blind, randomised, placebo controlled study of the pharmacokinetics of dronedarone in healthy male and female elderly subjects compared with young male subjects. The study treatment was dronedarone 200 mg capsules, administered as a 800 mg single dose and as a once daily administration, orally, for 12 days. Administration was in the fed state. The study included 54 subjects in total: 18 healthy young male subjects aged 21 to 38 years; 19 healthy elderly male subjects aged 65 to 77 years; and 17 healthy elderly female subjects aged 65 to 80 years. The pharmacokinetic analysis indicated that systemic exposure to dronedarone was increased in the elderly males compared with young males by around 25%, and in elderly females compared with elderly males by around 50%. The PK parameters for SR35021 were similar in young and elderly males, but were increased by around 60% in elderly females compared with elderly males: ratio (95% CI) for  $C_{\max}$  1.61 (1.32 to 2.05) and for  $AUC_{0-12h}$  1.60 (1.29 to 1.98).

**Study POP2896** was a three centre, open label, comparative, two group study of the pharmacokinetics in patients with moderate hepatic impairment compared with healthy subjects. The study was terminated early due to difficulties with recruitment. The study treatment was dronedarone 400 mg tablets, one tablet once daily for 10 days, orally in the fed state. The study included three subjects, two males and one female, aged 34 to 44 years. Two subjects had hepatic

impairment (Child Pugh score 7).<sup>7</sup> Limited conclusions can be made because of the small numbers, but although systemic exposure appeared to be similar for dronedarone, the exposure to SR35021 appears to be decreased in hepatic impairment, indicating a decrease in metabolism of dronedarone to SR35021.

**Study POP5820** was a two centre, open label, comparative, two parallel group study of the pharmacokinetics of dronedarone in patients with moderate hepatic impairment compared to healthy volunteers. The study treatment was dronedarone 400 mg tablets as either 400 mg once daily for 7 days, or 400 mg twice daily for 7 days. Administration was oral, in the fed state. The study included 26 subjects, and 24 completed the study and were included in the pharmacokinetic analysis. There were four healthy and four hepatic impaired subjects in the 400 mg once daily group, and eight healthy and eight hepatic impaired subjects in the 400 mg twice daily group. Of the 26 subjects included in the safety analysis, there were 16 males and 10 females. The age range was 45 to 69 years. The hepatic impaired subjects had a Child-Pugh score of 7 to 9. In hepatic impaired subjects, there was a non significant increase in  $C_{max}$ , ratio (95% CI) of 1.2 (0.63 to 2.28) for dronedarone once daily and 1.3 (0.75 to 2.33) for dronedarone twice daily. There was a two fold increase in unbound fractions of dronedarone in the hepatic impaired subjects. For SR35021, decreases in  $C_{max}$  and AUCs of around 50% were observed in hepatic impaired subjects compared with healthy subjects.

**Study PDY5850** was a four centre, randomised, placebo controlled, double blind study of the effect of dronedarone on creatininaemia and the pharmacokinetics of dronedarone in renal impairment. The study treatment was dronedarone 400 mg twice daily for 14 days and was compared to placebo. The study included 33 elderly male subjects divided into three groups on the basis of creatinine clearance: >30 to 50 mL/min; >50 to 80 mL/min and >80 mL/min. There were 12 subjects in the placebo group and 21 subjects in the active group. The age range was 65 to 79 years. Dronedarone and SR35021 pharmacokinetics were not altered by renal function.

#### *Evaluator's comment*

Systemic exposure to dronedarone is increased in the elderly males compared with young males by around 25%, and in elderly females compared with elderly males by around 50% (Study POP2769). There is no significant effect of hepatic impairment upon dronedarone exposure, but exposure to SR35021 is decreased in hepatic impairment (Study POP5820, Study POP2896). Dronedarone and SR35021 pharmacokinetics are not altered by renal impairment (Study PDY5850).

#### **Population Pharmacokinetic Studies**

**Study POH0203** was a population pharmacokinetic study of data from the ADONIS, EURIDIS, and ANDROMEDA studies to study covariate effects on dronedarone pharmacokinetics. The study was conducted by Sanofi-Aventis Modelling and Simulation. The study treatment was dronedarone 400 mg twice daily, oral administration, for up to 12 months. The study included data from 849 patients: 292 from ADONIS, 330 from EURIDIS, and 227 ANDROMEDA. The study included patients with atrial fibrillation, atrial flutter or congestive heart failure (NYHA class II to IV), and moderate to severe left ventricular dysfunction (wall motion index  $\leq 1.2$ ). The study population included 96 (31.0%) females; 214 (69.0%) males; age range 20 to 90 years; and 108 (9.5%) subjects co-medicated with CYP3A4 inhibitors. However, the CYP3A4 inhibitors were predominantly moderate rather than strong CYP3A4 inhibitors. The base model was a two-compartment model without lag time, with a combined error model and a log-normal distribution for all parameters. The absorption rate constant ( $k_a$ ) was fixed to the initial value (0.291 h,  $t_{1/2abs}$ : 2.38 h). Posthoc

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<sup>7</sup> The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

values for CL/F and V2/F were calculated and plotted against covariates. The final pharmacostatistical model was:

$$\text{CL/F (L)} = [301 \times (\text{WGT (Kg)} / 83)^{0.500}] \times (\text{AGE (y)} / (-12.1 + \text{AGE}))$$

The difference for CL/F between males and females was quantified as:

$$\text{CL/F (L/h) for females patients} = 0.827 \times \text{CL/F (L/h) of male patients}$$

The highest value of the correlation between parameter estimates was 0.92. The standard errors of parameter estimates were small enough so that 95% CIs did not include zero and all CV were below 50% (ranged between 4.0 and 19% for parameter estimates and from 2.5 and 14% for inter and intra-individual variabilities).

The study concluded that inter-patient variability in dronedarone clearance, central volume and peripheral volume in patients were about 30, 110 and 70%, respectively. The residual (intraindividual) variability was about 14 ng/mL. There was 16% lower clearance in female than in male patients. The clearance of dronedarone decreased with decreasing body weight. Clearance of dronedarone decreased with increasing age. Renal function, congestive heart failure degree, moderate CYP3A4 inhibitor co-administration and race were not found to influence the pharmacokinetics of dronedarone.

**Study POH0204** was a population pharmacokinetic study of data from the ADONIS, EURIDIS, and ANDROMEDA studies to study the covariate effect of creatinine clearance on dronedarone pharmacokinetics. The study treatment for all three studies was dronedarone 400 mg twice daily, oral administration, for up to 12 months. The study included 849 patients: 292 from ADONIS, 330 from EURIDIS, and 227 ANDROMEDA. The patients had atrial fibrillation, atrial flutter or congestive heart failure (NYHA class II to IV) and moderate to severe left ventricular dysfunction (wall motion index  $\leq 1.2$ ). Creatinine clearance was tested for inclusion on dronedarone CL/F as:

- a continuous covariate,
- a 4-class categorical covariate defined by the degree of renal impairment (RI) i.e., severe RI:  $\text{CLCR} < 30 \text{ mL/min}$ , moderate RI:  $30 < \text{CLCR} < 50 \text{ mL/min}$ , mild RI:  $50 < \text{CLCR} < 80 \text{ mL/min}$  and normal RF:  $\text{CLCR} > 80 \text{ mL/min}$ ),
- a series of binary variables, in order to maximize the chance of detecting and quantifying the impact of RI.

The covariates were added to the final model from Study POH0203.

For most of the codings, the inclusion of CLCR in the final PopPK model did not significantly increase the quality of the fit since the objective functional value (OFV) decrease for the successful runs was not significant (a decrease of 10.83 units was needed for  $p < 0.001$ ). When CLCR was treated as a binary variable, the inclusion of the covariate significantly decreased the OFV but the accuracy of the estimates was so poor (95% CIs including 0) that the inclusion of CLCR could not be supported.

### Other Pooled Analyses of Pharmacokinetic Data

**Study PMH0057** was a pooled analysis of data from Study TDU2164 and TDU3007. The study was a compartmental analysis of data for single intravenous doses of 40 mg, 60 mg and 80 mg administered to 26 healthy male volunteers. The study aimed to estimate the volume of distribution at steady state. The data were fitted to a two compartment, constant rate input and first order elimination model using WinNonLin. Dronedarone was found to have linear (dose proportional) pharmacokinetics at the dose levels used in the studies.

*Evaluator's comments:*

The population and pooled pharmacokinetic studies indicated that:

- There was 16% lower clearance in female than in male patients (Study POH0203).
- Clearance of dronedarone decreased with increasing age (Study POH0203).
- Creatinine clearance did not influence dronedarone clearance (Study POH0204).

## Drug Interactions

**Study INT2631** was a single centre, open label, randomised, two period, crossover, drug interaction study of the effects on the pharmacokinetics and pharmacodynamics of warfarin of dronedarone as multiple doses. The study treatments were: dronedarone 100 mg capsules, 400 mg once daily, for 13 days; and warfarin 10 mg tablets, 30 mg orally, two single doses before and at the end of 13 days treatment with dronedarone. The study included 14 healthy male volunteers aged 19 to 37 years. Twelve subjects completed the study. There was a slight increase in dronedarone and SR35021 C<sub>max</sub> and AUC with warfarin treatment. There were no changes in warfarin pharmacokinetics with dronedarone treatment. There was a mean increase in prothrombin time of one second in the group treated with dronedarone, but this was confounded by a carry-over effect from the previous dose and a sequence effect.

**Study INT2634** was a single centre, open label, baseline controlled sequential study of the effect of dronedarone on steady state digoxin pharmacokinetics, and upon ECG parameters in digoxin treated patients. The study treatments were: dronedarone 100 mg capsules, 400 mg once daily for 7 days, orally under fed conditions and digoxin 0.25 mg tablets: 0.75 mg on Day 1, then 0.25 mg daily, orally under fed conditions. Subjects were treated with digoxin for 14 days in total, the first 7 days being digoxin alone and the second 7 being digoxin and dronedarone in combination. The study included 13 healthy male volunteers aged 20 to 33 years. Twelve subjects completed the study. Dronedarone increased digoxin C<sub>max</sub> by 17% and AUC by 27%.

**Study INT2636** was a single centre, open-label study of the effect of propranolol pharmacokinetics and pharmacodynamics at steady state. The study treatments were dronedarone 100 mg capsules, 800 mg orally as a single dose, and as once daily for 7 days; and propranolol 40 mg tablets, 80 mg as a single dose and once daily for 14 days. The study included 19 healthy male volunteers aged 20 to 36 years. Sixteen subjects completed the study. Propranolol C<sub>max</sub> and AUC were increased by dronedarone in steady state. Steady state plasma concentrations of propranolol were increased by 16% to 33%. It is not clear whether the accumulation of dronedarone over 7 days was increased by propranolol or whether this reflected normal dronedarone pharmacokinetics.

**Study INT2931** was a single centre, double blind, placebo controlled study of the tolerability of ascending doses of dronedarone co-administered with stable doses of propranolol. The study treatments were:

- Dronedarone 100 mg capsules: 100, 400 or 800 mg once daily, for 2 days for each dose, orally under fed conditions for the 3 doses (6 days in total)
- Propranolol 400 mg tablets. 800 mg once daily orally for 7 days

The study included eight healthy male volunteers aged 20 to 30 years. Six subjects completed the study and two subjects discontinued: one for personal reasons, one due to intercurrent illness. Five subjects were treated with dronedarone, and three with placebo. Trough dronedarone and SR35021 concentrations in subjects receiving dronedarone were measured, but there were insufficient data to enable calculation of pharmacokinetic parameters.

**Study INT3353** was a single centre, open label, randomised, two period, crossover study of the effect of dronedarone on the pharmacokinetic and pharmacodynamic profile of warfarin; and of warfarin on the pharmacokinetic profile of dronedarone. The study treatments were:

- Dronedarone 200 mg capsules; 600 mg twice daily, orally for 14 days, administered orally in the fed state
- Warfarin 10 mg tablets; 30 mg once daily orally for two single doses (with and without dronedarone co-administration)

The study included 17 healthy male volunteers aged 26 to 45 years. Sixteen subjects completed the study. The pharmacokinetic parameters of either drug were unaffected by co-administration. There was a slightly higher International Normalised Ratio (INR) when warfarin was administered concurrently with dronedarone but this was not clinically significant. Hence some minor dosing adjustments may be required to warfarin dosing subsequent to commencing patients on dronedarone

**Study INT3560** was a single centre, open-label, randomised, two treatment, two period crossover study of the effect of pantoprazole on the pharmacokinetic profile of dronedarone administered in the fed state. The study treatments were:

- Dronedarone 400 mg tablets, 400 mg twice daily, oral administration in the fed state. There were two dosing periods of 7 days with 10 day washout period between doses.
- Pantoprazole, 40 mg enteric coated tablets, 40 mg once daily orally for 7 days

The study included 18 healthy male volunteers aged 21 to 40 years. Seventeen subjects completed the study. There was no significant effect of pantoprazole upon dronedarone pharmacokinetics.

**Study INT3561** was a single centre, non-randomised, open-label, two period study of the effect of ketoconazole on the pharmacokinetics and pharmacodynamics of dronedarone. The study included ECG and Holter monitoring. The study medications were:

- Dronedarone 100 mg capsules; 100mg or 200 mg once daily, orally, two single doses in the fed state, 13 day washout period between doses
- Ketoconazole 200 mg tablets, 200 mg once daily, orally for 8 days

The study included 12 healthy male volunteers aged 22 to 38 years. All 12 subjects completed the study. There were six subjects in the 100 mg group and six in the 200 mg group. Co-administration with ketoconazole resulted in greatly increased  $C_{max}$  and AUC for dronedarone.

**Study INT3683** was a single centre, non-randomised, open-label, single group, two period study of the effect of rifampicin on the pharmacokinetics and pharmacodynamics of dronedarone. The study treatments were:

- Dronedarone 200 mg tablets; 1400 mg once daily, two single doses, orally in the fed state
- Rifampicin 300 mg capsules, 600 mg orally once daily for 8 days

The study included 12 healthy male volunteers aged 19 to 31 years. Eleven subjects completed the study. Rifampicin co-administration significantly decreased the  $C_{max}$  and AUC of dronedarone. This interaction would be of major clinical significance.

**Study PDY3828** was a single centre, randomised, double blind, placebo controlled, dose escalation study of the pharmacokinetic and pharmacodynamic interaction between dronedarone and metoprolol. Monitoring was performed using Doppler echocardiography, exercise tests, ECG and Holter monitor. The study treatments were

- Dronedarone 200 mg tablets, 400, 600 or 800 mg twice daily for 8 days, orally in the fed state
- Placebo, twice daily

All study subjects received metoprolol 200 mg tablets, 200 mg once daily, orally for 13 days. The study included 49 healthy male volunteers aged 24 to 40 years. Forty four subjects completed. There were 13 subjects in the placebo group, six in the dronedarone 800 mg group (400 mg twice

daily), nine in the 1200 mg group and 20 in the 1600 mg group. There was a clinically significant increase in metoprolol plasma concentrations with co-administration of dronedarone.

**Study INT4074** was a single centre, non-randomised, open-label, sequential design, two period study of the effect of nifedipine and diltiazem on the pharmacokinetic profile of dronedarone. The study treatments were:

- Dronedarone 400 mg tablets, 400, 800, 1200, or 1600 mg once daily oral as two single doses in the fed state
- Nifedipine SR 20 mg tablets, 20 mg twice daily for 5 days
- Diltiazem SR 240 mg capsules; 240 mg twice daily oral for 5 days

The study plan was for six days of treatment: a single dose of dronedarone followed by 5 days of nifedipine or diltiazem, with co-administration of the second dose on Day 6. The study included 30 healthy male volunteers aged 20 to 40 years. All 30 subjects completed the study. There were twelve subjects in the 400 mg group, six in the 800 mg, six in the 1200 mg and six in the 1600 mg. There was a clinically significant increase in plasma concentrations of dronedarone with co-administration of diltiazem or nifedipine.

**Study INT4442** was a single centre, open-label, randomised, two treatment by two period crossover study of the effect of dronedarone on the pharmacokinetic profile of simvastatin. The study treatments were:

- Dronedarone 400 mg tablets, 1200 mg twice daily for 10 days, oral administration in the fed state
- Simvastatin 20 mg tablets, 20 mg once daily orally, two single doses. The first dose prior to dronedarone treatment, and the second during dronedarone treatment.

The study included 16 healthy male volunteers aged 23 to 40 years. Twelve subjects completed the study. Dronedarone co-administration resulted in a large and clinically significant increase in the plasma concentration of simvastatin.

**Study INT4695** was a single centre, randomised placebo controlled 2x2 crossover study of the effect of dronedarone on plasma concentrations of ethinylestradiol and levonorgestrel. The study treatments were:

- Dronedarone 200 mg tablets, 800 mg twice daily for 10 days, oral administration in the fed state
- Stediril 30 tablets: ethinylestradiol 0.03 mg and levonorgestrel 0.15 mg, once daily oral administration, two dosing cycles of 21 days

The study included 21 healthy female volunteers aged 18 to 37 years. Eighteen subjects completed the study. The plasma concentrations of ethinylestradiol and levonorgestrel were increased slightly by co-administration of dronedarone.

**Study INT4880** was a single centre, open-label, randomised, three treatment, three period crossover study of the pharmacokinetic interactions between dronedarone and simvastatin. The study consisted of three dosing periods with 7 to 13 day washout periods between each dosing period. The dosing periods were: dronedarone alone, simvastatin alone, and co-administration. The study treatments were:

- Dronedarone 400 mg tablets; 400 mg twice daily for two 14 day periods, oral administration in the fed state
- Simvastatin 20 mg tablets, 40 mg once daily for two 14 day periods, oral administration

The study included 24 healthy male volunteers aged 20 to 35. Twenty three subjects completed the study. Simvastatin decreased dronedarone plasma concentrations to a minor extent. Dronedarone

co-administration resulted in a large and clinically significant increase in the plasma concentrations of simvastatin.

**Study INT4881** was a single centre, open label, randomised, three treatment pharmacokinetic interaction study between dronedarone and nisoldipine. The study consisted of three treatment periods: dronedarone alone, nisoldipine alone and co-medication. The study treatments were:

- Dronedarone 400 mg tablets: 400 mg twice daily, orally in the fed state, for 14 days for two separate dosing periods
- Nisoldipine 20 mg tablets, 20 mg orally, once daily for 14 days, for two separate dosing periods

There was a 7 to 13 day washout period between doses. The study included 28 healthy male volunteers aged 19 to 34 years. Twenty six subjects completed the study. Plasma concentrations of dronedarone were increased slightly by nisoldipine. Nisoldipine plasma concentrations were greatly increased by dronedarone. There was an increase in QTc and PR interval with dronedarone, unaffected by nisoldipine.

**Study INT4882** was a single centre, open label, three treatment, three period, crossover study of the pharmacokinetic interactions between dronedarone and verapamil. The three treatment periods were: dronedarone alone, verapamil alone and co-administration. The study treatments were:

- Dronedarone 400 mg tablets, 400 mg twice daily, oral administration, for two 14 day periods
- Verapamil SR 120 mg tablets, 240 mg once daily, oral administration, for two 14 day period

There was a 7 to 14 day washout period between the treatment periods. The study included 21 healthy male volunteers aged 22 to 40. Nineteen subjects received study treatment and 18 completed the study. Dronedarone and verapamil increased each other's plasma concentrations by around 40% which is clinically significant.

**Study INT4884** was a single centre, open label, randomised, three treatment, three period, crossover study of the pharmacokinetic interactions between dronedarone and losartan. The three treatment periods were: dronedarone alone, losartan alone and co-administration. The study treatments were:

- Dronedarone 400 mg tablets, 400 mg twice daily, administered orally in the fed state, for two 14 day treatment periods
- Losartan 50 mg tablets; 100 mg once daily, oral administration, for two 14 day treatment periods

The study included 29 healthy male volunteers aged 18 to 40 years. All 29 subjects completed the study. There was a slight decrease in dronedarone plasma concentrations with losartan, but no significant effect of dronedarone upon losartan plasma concentrations.

**Study INT4886** was a single centre, randomised, open-label, two treatment, two period crossover study of the effect of grapefruit juice upon the pharmacokinetics of dronedarone. The study treatments were:

- Dronedarone 400 mg tablets, Two treatment phases of: 400 mg as two single doses (fasted and fed), and as a twice daily oral dose (in the fed state) for 10 days
- Grapefruit juice, double strength, 300 mL three times daily, orally, during one of the treatment phases

The study included 24 healthy male volunteers aged 18 to 39 years. Twenty subjects completed the study. Grapefruit juice co-administration resulted in a marked increase in dronedarone levels (around 2.5 to 4 fold increase) under fasted, fed and steady state conditions. SR35021 plasma concentrations were decreased concurrent with grapefruit juice administration, indicating inhibition of the CYP3A4 mediated metabolism of dronedarone. This effect is clinically significant.

**Study INT5084** was a single centre, randomised, double blind, placebo controlled, two sequence, two treatment, two period, crossover of the effect of dronedarone on the pharmacokinetics of theophylline. The study treatments were:

- Dronedarone 400 mg; 400 mg twice daily for 10 days, oral administration under fed conditions
- Theophylline 400 mg tablets, 400 mg twice daily, oral administration for two 10 day periods

The study included 39 healthy male volunteers aged 18 to 39 years. Twenty nine subjects completed the study. There was a reduction in theophylline plasma concentrations with dronedarone co-administration of approximately 17%. This can be taken to represent induction of CYP1A2.

**Study INT5139** was a single centre, randomised, double blind, placebo controlled, two sequence, two treatment, two period crossover study of the effect of dronedarone on the pharmacokinetic profile of digoxin. The study treatments were:

- Dronedarone 400 mg tablets; 400 mg twice daily, orally administered in the fed state, for 10 days
- Digoxin 0.25 mg tablets: loading dose of 0.75 mg on Day 1, the 0.25 mg daily for 9 days; two 10 day treatment periods

The study included 20 healthy male volunteers aged 18 to 39 years. Nineteen subjects completed the study. Digoxin clearance was decreased by 43%,  $C_{max}$  was increased by 75% and AUC by 157% by co-administration with dronedarone. This represents a clinically significant increase in exposure to digoxin with dronedarone co-administration.

#### *Evaluator's comments*

- Dronedarone resulted in a number of clinically significant pharmacokinetic interactions.
- Dronedarone increases digoxin maximum plasma concentrations ( $C_{max}$ ) by 17% when given at a dose of 400 mg once daily and by 75% when given at a dose of 400 mg twice daily, which is the recommended dosing regimen (Study INT2634, Study INT5139).
- Dronedarone increases plasma concentrations of propranolol by 16% to 33% (Study INT2636).
- Dronedarone increases verapamil plasma concentrations by around 40% (Study INT4882).
- Dronedarone increases plasma concentrations of metoprolol (Study PDY3828), simvastatin (Study INT4442, Study INT4880) and nisoldipine (Study INT4881).
- Plasma concentrations of ethinyloestradiol and levonorgestrel are increased slightly by co-administration of dronedarone (Study INT4695) as are those of losartan (Study INT4884).
- Dronedarone reduces theophylline plasma concentrations by 17% (Study INT5084).
- Dronedarone had no clinically significant effect upon warfarin pharmacokinetics, and a slight increase in INR (Study INT2631, Study INT3353).
- Ketoconazole markedly increases plasma concentrations of dronedarone (Study INT3561).
- Grapefruit juice co-administration results in a 2.5 to 4 fold increase in dronedarone plasma concentrations (Study INT4886).
- Verapamil increases dronedarone plasma concentrations by around 40% (Study INT4882).
- Plasma concentrations of dronedarone were significantly increased by both diltiazem and nifedipine (Study INT4074) and increased slightly by nisoldipine (Study INT4881).
- Rifampicin significantly decreases plasma concentrations of dronedarone (Study INT3683).
- There is no effect on dronedarone pharmacokinetics for pantoprazole (Study INT3560) or losartan (Study INT4884).

#### **Pharmacodynamics**

**Study PDY5487** was a randomised, placebo controlled, double-blind, 2x2 crossover study of the effect of dronedarone on renal blood flow and renal cationic transport compared to placebo. Renal



clearances of sinistrin, creatinine, PAH, and N1-methylnicotinamide (NMN), ratio of renal creatinine and sinistrin clearances, ratio of renal NMN and PAH clearances, and systemic sinistrin clearance were analyzed using a linear mixed effect model. The study treatments were:

- Dronedarone 400 mg tablets, 400 mg twice daily, oral administration, for 7 days
- Placebo tablets

The study included twelve healthy male volunteers aged 19 to 38 years. All twelve subjects completed the study. Renal sinistrin clearance was not affected by dronedarone indicating that dronedarone does not affect glomerular filtration rate (GFR). The creatinine over sinistrin renal clearance ratio significantly changed from 1.4 on placebo to 1.2 on dronedarone suggesting an inhibition by dronedarone on renal tubular secretion of creatinine. Dronedarone did not affect the renal PAH clearance, indicating no effect on renal blood flow and on the tubular organic anion transporter (OAT). The significant decrease of renal NMN clearance indicates that the tubular organic cation transporter (OCT) is inhibited by dronedarone. The renal creatinine clearance returned to baseline level after study drug discontinuation.

**Study PDY5923** was a randomised, placebo controlled, double blind, two parallel group study of the effects of dronedarone on creatininemia, plasma/urine markers of the renin-angiotensin system and associated factors including plasma renin activity, aldosterone, angiotensin II, cortisol, urea, uric acid, N1-methylnicotinamide, sodium, and potassium. The study treatments were:

- Dronedarone 400 mg tablets, 400 mg twice daily orally, for 14 days
- Placebo tablets, twice daily orally for 14 days

Both treatments had a three day placebo run-in period. The study included 31 healthy, young, male volunteers aged 20 to 39. There were ten subjects in the placebo group and 21 subjects in the dronedarone. There was a 15% increase in plasma creatinine in the dronedarone group compared to placebo, which persisted from Day 2 to end of treatment, then returned to normal. There were no treatment effects upon plasma or urine biomarkers of the renin angiotensin system.

**Study PDY2399** was a randomised, double blind, three ascending dose, four group pharmacodynamic study in patients with normal left ventricular function. The study included patients admitted for routine coronary angiography with normal left ventricular function and with non-critical coronary artery disease as assessed during the procedure or patients admitted for ablation of an accessory pathway and having undergone this ablation, with no evidence of critical coronary artery disease as assessed by past history, examination, electrocardiogram or previous angiogram. The study treatments were:

- Dronedarone 1 mg/mL mannitol solution; 20 mg, 40 mg, or 80 mg, administered intravenously over 1 hour as a single dose
- Amiodarone 3 mL vials, 5 mg/kg administered intravenously over 60 minutes as a single dose

The outcome measures were haemodynamic parameters of left ventricular function, and ECG parameters: heart rate, PQ, QRS, QTc, Wenckebach cycle length, atrial refractory period. The study enrolled 25 subjects, 21 were treated with study drug, and all 21 completed the study. The number of subjects in each study group was: amiodarone n=7, and dronedarone 20 mg n=6, 40 mg n=6, 80 mg n=2. Seventeen subjects were male, and four were female. The age range was 25 to 66 years, and all subjects were Caucasian.

Systolic, diastolic and mean pulmonary arterial pressures significantly increased in the amiodarone group at both T30 and T60. No significant changes were observed in any of the dronedarone treatment groups. For all three of these parameters there was a statistically significant difference between the treatment groups at T30. There was a decrease in pulmonary vascular resistance in the dronedarone groups, which was dose-related. A statistically significant decrease was observed for

the peak positive dp/dt (derivative of left ventricular pressure (LVP)) in the amiodarone treated group at T60, and an increase in the peak negative dp/dt in the amiodarone treated group at T30. There was a decrease in heart rate at T30 in the dronedarone 20 mg group: mean (standard deviation [SD]) 4 (3.5) beats per minute (bpm). There was a slight increase in QT interval in the dronedarone 20 mg group at T30. There were no significant changes in electrophysiology in the dronedarone groups at T60. There was no significant difference between the groups in right atrial pressure, systemic arterial parameters, pulmonary capillary wedge pressure.

**Study PDY2400** was a single centre, open label, sequential three group study of the electrophysiological effects and haemodynamic parameters in patients with impaired left ventricular function treated with dronedarone. The study included patients with impaired left ventricular function (LVF) and with documented or suspected coronary artery disease. The outcome measures were: electrophysiology: measurement of conduction intervals, atrial, atrioventricular (AV)-nodal and ventricular parameters during pacing and right ventricular monophasic action potential parameters; haemodynamics: LVF parameters; and tolerability: adverse events (AEs), electrocardiogram (ECG) and laboratory tests. The study treatment was dronedarone 20 mg, 40 mg or 80 mg single dose as a 60 minute intravenous infusion. The study included 23 male patients with impaired left ventricular function, age range 41 to 77 years. All 23 patients completed. There were eight patients in the dronedarone 20 mg group, seven in the 40 mg group and eight in the 80 mg group. There was no significant effect of dronedarone on: heart rate, RR interval, PQ, QRS, QTc, or QT. There was no change in Wenckebach cycle length, atrial refractory period or atrioventricular nodal refractory period. During pacing there was an overall longer duration in QT of 3.6 milliseconds (ms) ( $p=0.0181$ ). There was no significant effect on right ventricular MAP. There was a decrease in cardiac output in the 40 mg group. There was no change in systemic blood pressure or pulmonary artery pressure. There was a significant increase in pulmonary wedge pressure. There was a significant decrease in systolic left ventricular pressure, left ventricular end diastolic pressure, peak positive dp/dt and peak negative dp/dt. At the 40 mg dose there was a significant decrease in cardiac output at T30 of mean (95% CI) -0.36 (-0.61 to -0.11) L/min ( $p=0.0360$ ) and at T60 of -0.47 (-0.78 to -0.17) L/min ( $p=0.0291$ ).

**Study ACT2401** was a multicentre, double blind, randomised, placebo controlled, ascending dose study in three sequential groups to investigate the effects on walking distance, ejection fraction, New York Heart Association (NYHA) status, hepatic and renal functions and on Holter parameters. The study included patients with known impaired left ventricular function of any cause (LVEF  $\leq 30$  %), who were stabilized with either asymptomatic or mildly symptomatic heart disease (NYHA class I and II), and who were on well conducted treatments with angiotensin-converting enzyme inhibitors (ACEIs), diuretics, digoxin and possibly nitrates. The study treatment was dronedarone 100 mg and 200 mg capsules. The dose groups were: 400 mg once daily, 800 mg once daily or 600 mg twice daily. The comparator was placebo. The treatments were administered orally for one month. The primary endpoint: walking distance, measured during a "standardized" 6-minute walk test of submaximal exercise capacity after one month of treatment. Secondary endpoints were: LVEF (radionuclide ventriculography) and cardiothoracic ratio (chest X-ray). The safety endpoints were AEs, clinical laboratory tests, vital signs, 12 lead ECG and Holter monitor.

The study enrolled and treated 124 patients and 111 completed. There were 110 males and 14 females. The age range was 25 to 80 years. There were 40 patients in the placebo group, 29 in the 400 mg, 30 in the 800 mg and 25 in the 1200 mg. There was no significant between group difference in 6-minute walk test, LVEF, cardiothoracic ratio or change in NYHA classification. The global incidence of QTc prolongation was similar in all three groups: 16 (40%) for placebo, 10 (34.5%) for 400 mg, 14 (46.7%) for 800 mg and 12 (52.0%) for 1200 mg. There was a decrease in the number of supraventricular extrasystoles in the dronedarone groups that was dose dependent.

**Study PDY2402** was a multicentre, randomised, open-label, three parallel group study of the electrophysiological effects and haemodynamic parameters of dronedarone compared with amiodarone. The study included twelve patients with normal or impaired left ventricular function. All twelve subjects completed the study. There were five male and seven female subjects, their age range was 44 to 69 years, and seven of the twelve subjects had normal left ventricular ejection fraction (LVEF). There were four subjects in the 400 mg group, four in the 800 mg group and four in the amiodarone group. A total of 75 patients were planned but the study was terminated because of slow recruitment. The study included male patients or surgically sterile or post-menopausal females who were admitted to the clinical unit for routine catheterization with normal or impaired LVEF of any cause. The study treatments were:

- Dronedarone 200 mg capsules; 400 mg or 800 mg once daily, oral administration for 28 days
- Amiodarone 200 mg tablets; 400 mg once daily for 28 days

The outcome measures were: heart rate, PQ, QRS, QTC, PA, AH, HV intervals, atrial effective refractory period (AERP) and ventricular effective refractory period (VERP). LVEF parameters were measured in subjects with impaired LVEF (LVEF 20% - 40%); physical examination, electrocardiogram (12-lead and Holter) and laboratory tests. The data were limited due to early termination of the study. Haemodynamic assessments were performed in only 4 of the 5 randomised patients with impaired LVEF.

#### *Evaluator's comments:*

The tubular organic cation transporter (OCT) is inhibited by dronedarone (Study PDY5487). There was a 15% increase in plasma creatinine in the dronedarone group compared to placebo (Study PDY5923). There was a dose related decrease in pulmonary vascular resistance in the dronedarone groups, a decrease in heart rate and a slight increase in QT interval in the dronedarone 20 mg group (Study PDY2399).

Intravenous dronedarone resulted in a decrease in systolic left ventricular pressure, left ventricular end diastolic pressure, peak positive dp/dt, peak negative dp/dt, and at the 40 mg dose there was a significant decrease in cardiac output (Study PDY2400). However, in a study of oral dronedarone compared with placebo there was no significant between group difference in 6-minute walk test, LVEF, cardiothoracic ratio or change in NYHA classification.

## **Efficacy**

### **Placebo Controlled Studies**

**Study DRI3550 DAFNE** was a double blind, placebo controlled, parallel group, dose ranging study of dronedarone for the maintenance of sinus rhythm after cardioversion (Table 2). The study was conducted in 50 centres in eleven countries in Europe and Israel. The inclusion criteria included

- Patients of either sex aged 21 to 85 years with persistent AF (>72 hours and <12 months duration) for whom cardioversion and antiarrhythmic treatment was warranted.
- The AF could be unassociated with structural heart disease (lone AF) or associated with ischemic, hypertensive, haemodynamically insignificant primary valvular heart disease or dilated cardiomyopathy (left ventricular ejection fraction had to be  $\geq 35\%$ ).

The exclusion criteria included:

- Women of child-bearing potential (only post-menopausal and/or sterilized women could be included);
- Documentation of atrial flutter as the presenting arrhythmia;
- Unstable angina pectoris
- AF associated with an acute reversible condition

- Plasma potassium <3.5 mmol/L and uncorrected or >5.5 mmol/L;
- Congenital long QT syndrome;
- QT-interval >500 ms;
- History of torsades de pointes;
- Bradycardia <50 bpm while awake;
- Evidence on electrocardiograms (ECG) recorded in sinus rhythm of PR-interval  $\geq 0.28$  s or high degree atrioventricular block (second degree or higher), or significant sinus node disease without a permanent pacemaker implanted;
- Antiarrhythmic therapy required for other arrhythmias;
- Treatment with other antiarrhythmic drugs: amiodarone for 5 or more days during the last 6 months; or patients who have received intravenous amiodarone for  $\geq 5$  days during the last 6 months could be included after a wash-out period of 5 days;
- All other antiarrhythmic drugs were withdrawn for at least five plasma half-lives before the beginning of the study;
- Clinically overt congestive heart failure or New York Heart Association (NYHA) class III or IV;
- Left ventricular ejection fraction less than 35% assessed by radionuclide angiography or echocardiography within the 4 weeks preceding the screening visit;
- Evidence of clinically relevant haematologic, hepatic (alanine aminotransferase [ALT], aspartate aminotransferase (AST), bilirubin >2 times the laboratory upper limit), gastro-intestinal, renal (plasma creatinine >150  $\mu\text{mol/L}$ ), pulmonary, endocrinologic (in particular thyroid) or psychiatric disease;
- Potentially dangerous symptoms associated with AF such as angina pectoris, transient ischemic attacks, stroke, syncope precluding the ethical administration of placebo;
- Wolff-Parkinson-White syndrome;
- Patients with an implantable cardioverter defibrillator;
- More than two cardioversions in the last 6 months;
- Contraindication to oral anti-coagulant.

The study treatments are indicated in Table 2. The primary endpoint was the time to first recurrence of AF after conversion to sinus rhythm, that is, maintenance time, as measured by 12-lead ECG, trans-telephonic ECG monitoring (TTEM), or telemetry. Secondary efficacy endpoints were:

- Time to AF treatment failure from randomization
- Number of patients converted at or before Visit 2 (V2) by non-electrical means
- Total number of patients converted at or before V2
- Cardioversion procedure characteristics
- Ventricular rate in case of AF recurrence
- Symptoms on treatment
- ECG parameters during the maintenance period

Safety outcome measures were: AEs, ECG, vital signs and laboratory safety tests. Hypothesis tests were performed using ANOVA and Kaplan Meier plots.

A total of 270 subjects were enrolled and treated, and of these 240 completed. Of the enrolled subjects, 269 were Caucasian, 182 were male, 88 were female and the age range was 24 to 81 years. There were 76 subjects randomised to the 400 mg group, 66 to the 600 mg; 62 to the 800 mg and 66 to the placebo. The treatment groups were similar in baseline demographic characteristics. A greater proportion of patients withdrew because of AEs in the dronedarone groups, with a dose dependent effect. In the intention to treat analysis there was a statistically significant increase in time to first AF recurrence for the 400 mg twice daily treatment, compared with placebo but not for

the other two treatment groups. A similar effect was observed for time to treatment failure. There was an increasing proportion of patients reverting without electrical cardioversion with increasing dronedarone dose. Ventricular rate in case of recurrence was lower in the dronedarone groups. There was no difference between the groups in the number of DC shocks required for cardioversion and no difference in the energy (in Joules) required for cardioversion. The PR-interval was longer by 13.4, 16.6, and 28.4 ms in the 800, 1200 and 1600 mg groups respectively, ( $p=0.0031$ , ANOVA). QTc intervals were prolonged in the 800 mg twice daily group ( $p=0.0024$ ).

Table 2. Details of Study DRI3550 DAFNE

Design	Nr of subjects with age and sex Duration	Diagnosis + criteria for inclusion/exclusion	Test Product/ Reference therapy Dosage Regimen Route of administration, Formulation	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Double blind, placebo controlled, parallel group, dose ranging study of dronedarone for the maintenance of sinus rhythm after cardioversion	270 subjects enrolled and treated 240 completed 269 Caucasian 182 male, 88 female Age range 24 to 81 years  76 in the 400 mg group, 66 in the 600 mg; 62 in the 800 mg and 66 in the placebo 6 months	Patients undergoing cardioversion for atrial fibrillation  Patients of either sex aged 21 to 85 years with persistent AF (>72 hours and <12 months duration) for whom cardioversion and antiarrhythmic treatment was warranted.  The AF could be unassociated with structural heart disease (lone AF) or associated with ischemic, hypertensive, haemodynamically insignificant primary valvular heart disease or dilated cardiomyopathy (left ventricular ejection fraction had to be $\geq 35\%$ ).	Dronedarone 200 mg tablets 400 mg, 600 mg, or 800 mg twice daily, oral administration, in the fed state  Patients were commenced on treatment on Day 1 and cardioversion was performed on Day 5 to Day 8  An oral anti-coagulant was started 3 weeks before Day 1 and was continued at least 4 weeks following cardioversion.  Placebo tablets, twice daily, oral administration	The primary endpoint was the time to first recurrence of AF after conversion to sinus rhythm, i.e., maintenance time, as measured by 12-lead ECG, TTEM, or telemetry.  Secondary endpoints were: Time to AF treatment failure from randomization  Number of patients converted at or before Visit 2 (V2) by non-electrical means  Total number of patients converted at or before V2  Cardioversion procedure characteristics  Ventricular rate in case of AF recurrence  Symptoms on treatment  ECG parameters during the maintenance period	There was a statistically significant increase in time to first AF recurrence for the 400 mg twice daily treatment, compared with placebo but not for the other two treatment groups  A similar effect was observed for time to treatment failure  There was an increasing proportion of patients reverting without electrical cardioversion with increasing dronedarone dose  Ventricular rate in case of recurrence was lower in the dronedarone groups The PR-interval was longer by 13.4, 16.6, and 28.4 ms in the 800, 1200 and 1600 mg groups respectively, ( $p=0.0031$ , ANOVA). QTc intervals were prolonged in the 800 mg twice daily group ( $p=0.0024$ ).	TEAEs were reported by 56 (84.8%) subjects for placebo; 41 (80.3%) for 400 mg; 57 (86.4%) for 600 mg and 53 (85.5%) for 800 mg. The pattern of TEAEs was similar for the four treatment groups  There were similar numbers (%) discontinuing because of AEs: 40 (60.6%) for placebo; 36 (47.4%) for 400 mg; 40 (60.6%) for 600 mg and 38 (61.3%) for 800 mg. SAEs were more frequent at the higher dronedarone doses: 4 (4.5%) for placebo; 2 (2.6%) for 400 mg; 5 (7.6%) for 600 mg and 7 (11.3%) for 800 mg  There was one death: due to accidental trauma in the 800 mg group. More patients in the dronedarone groups had a decrease in haemoglobin, and increase in transaminases or increase in creatinine

TEAE= Treatment-Emergent Adverse Event

**Study EFC4508 ERATO** was a double blind, placebo controlled, parallel group efficacy study for the control of ventricular rate in patients with atrial fibrillation (Table 3). The study was conducted at 35 centres in nine European countries.

Inclusion criteria included:

- Patients of either sex aged 21 years or greater, with symptomatic permanent AF (defined as duration of AF > 6 months) for which cardioversion was not considered (symptomatic refers to any AF-related symptoms including palpitations);

- Resting ventricular rate  $\geq 80$  bpm at screening measured on a 6-second rhythm strip

The exclusion criteria included:

- Pregnant women or women of child-bearing potential not on adequate birth control;
- Breastfeeding women;
- Unstable angina pectoris: ischaemic symptoms during the last 7 days or recent myocardial infarction ( $< 6$  weeks)
- History of torsades de pointes;
- Plasma potassium  $< 3.5$  mmol/L at screening;
- Third degree AV block on the screening ECG while in AF or documentation of PR-interval on ECGs previously recorded while in sinus rhythm  $> 0.28$  seconds or high degree AV block (second degree or higher), or significant sinus node disease (documented pause of 3 seconds or more); without a permanent pacemaker implanted;
- Clinically overt congestive heart failure [New York Heart Association (NYHA) class III or IV] at randomization;
- Clinically relevant haematologic, hepatic [ALT, AST  $> 2$  times the upper limit of normal (ULN) at screening], gastrointestinal, renal (serum creatinine  $> 220$   $\mu$ mol/L at screening), pulmonary, endocrinologic (in particular thyroid) or psychiatric disease;
- Patients treated with amiodarone during the 2 months preceding randomization, these patients were included only after a washout period of 2 months;
- Treatment with other antiarrhythmic drugs;

The study treatments are shown in Table 3.

The primary efficacy outcome measure was the change in mean heart rate measured by a 24-hour Holter recording at rest on Day 14 (steady state) compared to baseline. The secondary efficacy outcome measures were:

- exercise tolerance on Day 14 compared to baseline (maximal exercise duration defined as time elapsed between the start of the exercise test and its stop).
- evaluation of exercise performance: difference in heart rate at sub-maximal and maximal exercise between baseline and Day 14;
- to document that exercise performance was not diminished by the expected decrease in heart rate:
  - difference for each gas exchange parameter and for systolic blood pressure (SBP) between baseline and Day 14 (at rest, sub-maximal, anaerobic threshold and maximal intensity);
  - difference for anaerobic threshold between baseline and Day 14 (duration in seconds from the beginning of the exercise test);
- difference in heart rate evaluated by the 24-hour Holter recording between baseline and Month 4.

Table 3. Details of Study EFC4508 ERATO

Design	Nr of subjects with age and sex Duration	Diagnosis + criteria for inclusion/exclusion	Test Product/ Reference therapy Dosage Regimen Route of administration, Formulation	Results (efficacy)	Adverse Reactions
Double blind, placebo controlled, parallel group efficacy study for the control of ventricular rate in patients with atrial fibrillation	185 patients enrolled, 11 excluded, 174 analysed, 147 completed 120 male, 54 female 172 Caucasian, 2 Black Age range 31 to 86 years  85 subjects in the dronedarone group and 89 in the placebo 6 months	Inclusion criteria:  Patients of either sex aged 21 years or greater, with symptomatic permanent AF (defined as duration of AF>6 months) for which cardioversion was not considered (symptomatic refers to any AF-related symptoms including palpitations);  Resting ventricular rate $\geq 80$ bpm at screening measured on a 6-second rhythm strip;  Exclusion criteria:  Pregnant women or women of child-bearing potential not on adequate birth control; Breastfeeding women; Unstable angina pectoris: ischemic symptoms during the last 7 days or recent myocardial infarction (<6 weeks)  History of torsades de pointes; Plasma potassium <3.5 mmol/L at screening;	Dronedarone 400 mg tablets: 400 mg twice daily, oral administration in the fed state  Placebo tablets	Dronedarone had greater efficacy than placebo for the primary outcome measure, with a greater decrease in ventricular rate at Day 14. There was no difference between the treatment groups in duration of maximal exercise. Heart rate at sub-maximal exercise was lower in the dronedarone group. Heart rate at maximal exercise was lower in the dronedarone group.  The decrease in heart rate in the dronedarone groups was maintained at Month 4. Eight (9.4%) patients in the dronedarone group and two (2.2%) patients in the placebo group experienced a conversion to sinus rhythm during the study	TEAEs were reported by 53 (59.6%) subjects in the placebo group and 65 (76.5%) in the dronedarone. SAEs were reported in 12 (13.5%) patients in the placebo group and 14 (16.5%) in the dronedarone. There was one death during the study in the dronedarone group and an additional two deaths after study treatment had finished. Withdrawals due to TEAE occurred for 9 (10.1%) patients in the placebo group and 13 (15.3%) in the dronedarone. There was a mean increase in serum creatinine in the dronedarone group of 10.6 $\mu\text{mol/L}$ . Digoxin levels increased by a mean of 41.4% in the dronedarone group. There was no apparent change in INR in the dronedarone group. Two patients in the placebo group and four in the dronedarone had elevations in AST >2xULN. Five patients in the placebo group and six in the dronedarone had elevations in ALT >2xULN.

Dronedarone had greater efficacy than placebo for the primary outcome measure, with a greater decrease in ventricular rate at Day 14. There was no difference between the treatment groups in duration of maximal exercise. Heart rate at sub-maximal exercise was lower in the dronedarone group. Heart rate at maximal exercise was lower in the dronedarone group. The change from baseline to Day 14 in SBP measured at rest and during sub-maximal exercise in the dronedarone group was significantly more pronounced than in the placebo group (at rest:

-7.0 mmHg versus 0.2 mmHg, ANCOVA,  $p=0.0146$ ; during sub-maximal exercise:

-9.2 mmHg versus -0.7 mmHg, ANCOVA,  $p=0.0174$ ).

There was no significant difference between the groups in change from baseline to Day 14 for SBP, measured at maximal exercise. The decrease in heart rate in the dronedarone groups was maintained at Month 4. There was no difference between the groups in gas exchange. Eight (9.4%) patients in the dronedarone group and two (2.2%) patients in the placebo group experienced a conversion to sinus rhythm during the study (including one patient in each group who underwent electrical cardioversion), but this difference was not statistically significant: Fisher's exact test  $p=0.053$ .

**Study EFC3153 EURIDIS** was a multicentre, multinational, double blind, placebo controlled, efficacy study of dronedarone for maintaining sinus rhythm after conversion of atrial fibrillation/atrial flutter (Table 4). Inclusion criteria were:

- Patients of either sex aged 21 years or greater, in sinus rhythm for at least 1 hour at the time of randomization and with at least 1 ECG-documented AF/AFL episode in the last 3 months.

The exclusion criteria included:

- women of childbearing potential not on adequate birth control or breast-feeding
- documented AF/AFL episode motivating inclusion in the study starting and not persisting beyond 10 days after an acute condition known to cause AF/AFL (for example, alcohol intake, thyrotoxicosis, infection, myocardial infarction, pericarditis, pulmonary embolism, cardiac surgery);
- history of torsades de pointes;
- bradycardia <50 bpm at the screening ECG;
- PR-interval  $\geq 0.28$  second at screening;
- high degree atrioventricular (AV) block (second degree or higher), or significant sinus node disease (documented pause of 3 seconds or more) without a permanent pacemaker implanted;
- treatment with other Class I or III antiarrhythmic drugs;
- clinically overt congestive heart failure (CHF) with New York Heart Association (NYHA) Class III or IV at the time of randomization;
- clinically relevant haematologic, hepatic [alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin >2 times the upper limit of normal (ULN) at screening], gastrointestinal (GI), renal [serum creatinine  $\geq 150$   $\mu\text{mol/L}$  at screening], pulmonary, endocrinologic (in particular thyroid) or psychiatric disease;
- ongoing potentially dangerous symptoms when in AF/AFL such as angina pectoris, transient ischemic attacks, stroke, syncope, as judged by the Investigator;
- patients in whom amiodarone prescribed for sinus rhythm maintenance was discontinued for inefficacy;
- patients in whom 3 or more Class I or III antiarrhythmic drugs prescribed for sinus rhythm maintenance were discontinued for inefficacy;
- patients known to have chronic AF/AFL, defined as continuous AF/AFL for more than 12 months;
- patients in whom a contraindicated concomitant treatment was mandatory;
- patients thought to be unable to use the TTEM system as scheduled in the study protocol;
- hypokalaemia (plasma potassium <3.5 mmol/L) and hypomagnesaemia (plasma magnesium <0.7 mmol/L) had to be corrected before inclusion

The study treatments are shown in Table 4.

The primary efficacy variable was: the time in days elapsed between randomization and the first documented AF/AFL recurrence within 12 months from randomization. An AF/AFL recurrence was defined as an episode lasting 10 minutes or more, as indicated by two consecutive 12-lead ECGs or TTEM tracings recorded approximately 10 minutes apart, both showing AF/AFL. The secondary efficacy variables were:

- symptomatic AF/AFL among the adjudicated first AF/AFL recurrence;
- ventricular rate assessed at the time of the adjudicated first AF/AFL recurrence;
- time elapsed in days between Day 5 midnight (steady state) and the adjudicated first AF/AFL recurrence within 12 months from randomization.

Hypothesis testing was performed using survival analysis and the log-rank test or Hazard Ratios.



Table 4: Details of *Study EFC3153 EURIDIS*

Design	Nr. Of subjects with age and sex	Duration of Treatment Reference therapy	Test Product Dosage Regimen Route of administration, Formulation	Results (efficacy)	Adverse Reactions
Multicentre, multinational, double blind, parallel group, placebo controlled, efficacy study of dronedarone for maintaining sinus rhythm after conversion of atrial fibrillation/atrial flutter	615 subjects enrolled, 612 treated and 520 completed 610 treated subjects were Caucasian 425 were male and 187 were female Age range was 23 to 86 years 411 subjects in the dronedarone group and 201 in the placebo	12 months Placebo tablets	Dronedarone 400 mg tablets: 400 mg twice daily, orally  Randomisation was performed using an IVRS  Patients were randomised to dronedarone or placebo in a 2:1 ratio	For the primary efficacy outcome variable, dronedarone had greater efficacy than placebo. Dronedarone decreased the risk of first recurrence on AF/AFL by 12 months by 22%. The risk of symptomatic first recurrence was also reduced over the 12-month follow up. Ventricular rate in first recurrence was lower in the dronedarone group. Time from steady state to first recurrence was greater in the dronedarone group	TEAEs were reported in 117 (58.2 %) subjects in the placebo group and 244 (59.4 %) in the dronedarone. The commonest TEAEs in the dronedarone group other than atrial fibrillation, were diarrhoea, headache, influenza and nasopharyngitis. SAEs were reported in 53 (26.4 %) subjects in the placebo group and 76 (18.5 %) in the dronedarone. There were two deaths during the study, both occurring in the dronedarone group: one sudden death; one myocardial infarction. Thirteen (6.5%) subjects in the placebo group and 35 (8.5%) in the dronedarone discontinued because of TEAEs. Serum creatinine increased by a mean of 8.8 µmol/L from Day 7 in the dronedarone group. Prolongation of the PR interval and prolongation of the QTc occurred more frequently in the dronedarone group.

For the primary efficacy outcome variable, dronedarone had greater efficacy than placebo. Dronedarone decreased the risk of first recurrence on AF/AFL by 12 months by 22%. The risk was decreased by Day 30 of treatment and maintained over the 12 month follow-up period. The risk of symptomatic first recurrence was also reduced over the 12-month follow up, log rank  $p=0.0055$ . Ventricular rate in first recurrence was lower in the dronedarone group, ANOVA  $p<0.0001$ . Time from steady state to first recurrence was greater in the dronedarone group.

**Study EFC4788 ADONIS** was a multicentre, multinational, double blind, placebo controlled, parallel group efficacy study of dronedarone for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter (Table 5). The study was conducted at 101 centres in the US, Canada, Australia, South Africa and Argentina.

The inclusion criteria were:

- Patients of either sex aged 21 years or greater, in sinus rhythm for at least 1 hour at the time of randomisation and with at least one ECG-documented AF/AFL episode in the last 3 months.

The exclusion criteria included:

- women of childbearing potential not on adequate birth control and/or breast-feeding
- documented AF/AFL episode motivating inclusion in the study starting and not persisting beyond 10 days after an acute condition known to cause AF/AFL (for example, alcohol intake, thyrotoxicosis, infection, myocardial infarction, pericarditis, pulmonary embolism, cardiac surgery);
- history of torsades de pointes;
- bradycardia  $<50$  bpm at the screening ECG;
- PR-interval  $\geq 0.28$  seconds at screening;
- high degree atrioventricular (AV) block (second degree or higher), or significant sinus node disease (documented pause of 3 seconds or more) without a permanent pacemaker implanted;
- treatment with other Class I or III antiarrhythmic drugs;

- clinically overt congestive heart failure (CHF) with New York Heart Association (NYHA) Class III or IV at the time of randomization;
- clinically relevant haematologic, hepatic (ALT, AST or bilirubin >2 times the upper limit of normal at screening), gastrointestinal, renal (serum creatinine  $\geq 150 \mu\text{mol/L}$ ), pulmonary, endocrinologic (in particular thyroid) or psychiatric disease;
- ongoing potentially dangerous symptoms when in AF/AFL such as angina pectoris, transient ischemic attacks, stroke, syncope;
- patients in whom amiodarone prescribed for sinus rhythm maintenance was discontinued for inefficacy;
- patients in whom three or more Class I or III antiarrhythmic drugs prescribed for sinus rhythm maintenance were discontinued for inefficacy;
- patients known to have chronic AF/AFL defined as continuous AF/AFL for more than 12 months;
- patients in whom a contraindicated concomitant treatment was mandatory;
- patients thought to be unable to use the TTEM system as scheduled in the study protocol;
- hypokalaemia (plasma potassium  $< 3.5 \text{ mmol/L}$ ) and hypomagnesaemia (plasma magnesium  $< 0.7 \text{ mmol/L}$ ) had to be corrected before inclusion

The study treatments are shown in Table 5.

Table 5. Details of Study EFC4788 ADONIS

Design	Nr of subjects with age and sex	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Results (efficacy)	Adverse Reactions
Multicentre, multinational, double blind, placebo controlled, parallel group efficacy study of dronedarone for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter	629 patients enrolled, 625 treated and 508 completed  433 male and 192 female  12 Black, 590 Caucasian and 23 other  Age range 20 to 88 years   417 treated with dronedarone and 208 with placebo	12 months duration	Dronedarone 400 mg tablets  400 mg twice daily, oral administration in the fed state   Randomisation and allocation to treatment group was performed using an IVRS	Placebo tablets, twice daily oral administration	For the primary efficacy outcome measure, dronedarone was superior to placebo. The treatment effect occurred from Day 30 and was maintained throughout the treatment period. The treatment difference was 11.7% at 12 months. Fewer subjects had symptomatic recurrence of AF/AFT in the dronedarone group. Heart rate at time of first recurrence was lower in the dronedarone group. Time from steady state to first recurrence was also lower in the dronedarone group.	TEAEs were reported in 152 (73.1 %) subjects in the placebo group and 334 (80.1 %) in the dronedarone. Excluding AF/AFL, TEAEs were reported in 149 (71.6 %) subjects in the placebo group and 326 (78.2 %) in the dronedarone. SAEs were reported in 47 (22.6 %) subjects in the placebo group and 88 (21.1 %) in the dronedarone. Death occurred for three (1.4 %) subjects in the placebo group and six (1.4 %) in the dronedarone. 16 (7.7%) subjects discontinued because of TEAEs in the placebo group and 45 (10.8 %) in the dronedarone

The primary efficacy outcome measure was the time in days elapsed between randomization and the first documented AF/AFL recurrence within 12 months from randomization. An AF/AFL recurrence was defined as an episode lasting 10 minutes or more, as indicated by two consecutive 12-lead ECGs or TTEM tracings recorded approximately 10 minutes apart, both showing AF/AFL, and confirmed by the ECG Corelab responsible for the adjudication of the first recurrence based on the analysis of all ECGs and/or TTEMs. The secondary efficacy outcome measures were:

- symptomatic AF/AFL among the adjudicated first AF/AFL recurrence;
- ventricular rate assessed at the time of the adjudicated first AF/AFL recurrence;
- time elapsed in days between Day 5 midnight (steady state) and the adjudicated first AF/AFL recurrence within 12 months from randomization.

Hypothesis tests were performed using the Log-rank test, cumulative incidence functions using the nonparametric Kaplan-Meier estimate, and Relative Risk (Hazard Ratio) with 95% confidence interval (CI) using a Cox model.

For the primary efficacy outcome measure, dronedarone was superior to placebo. The treatment effect occurred from Day 30 and was maintained throughout the treatment period. The treatment difference was 11.7% at 12 months. Fewer subjects had symptomatic recurrence of AF/AFL in the dronedarone group, Log-rank  $p=0.021$ . Heart rate at time of first recurrence was lower in the dronedarone group, ANOVA  $p=0.0009$ . Time from steady state to first recurrence was also lower in the dronedarone group. Peak and trough dronedarone plasma concentrations were measured and included in a population pharmacokinetic analysis. In addition to that analysis, it was found that the effect of dronedarone on time to first AF/AFL recurrence was highly significant ( $p = 0.0014$ ) in the high trough plasma concentration group, and significant ( $p = 0.0323$ ) in the low trough plasma concentration group. This finding suggests that therapeutic drug monitoring of trough dronedarone concentrations might be useful.

**Study EFC5555 ATHENA** was a multicentre, multinational, double blind, placebo controlled, parallel group study of the efficacy of dronedarone for the prevention of cardiovascular hospitalisation or death from any cause in patients with AF/AFL (Table 6). The study was conducted at 551 centres in 37 countries. The study was performed to investigate the effect of dronedarone on cardiovascular hospitalisation or all-cause mortality. Post-hoc analysis of previous studies (EURIDIS and ADONIS) had suggested a beneficial effect of dronedarone on cardiovascular hospitalisation or all-cause mortality, but ANDROMEDA had indicated an increased mortality in the dronedarone group. This increased mortality was postulated to be because of cessation of ACEI and angiotensin II receptor antagonists because of elevations in creatinine in the dronedarone group.

Inclusion criteria were:

- One or more of the following risk factors must be present at baseline:
  - Age equal to or greater than 70 years
  - Hypertension (taking antihypertensive drugs of at least 2 different classes)
  - Diabetes
  - Prior cerebrovascular accident (stroke or transient ischemic attack) or systemic embolism
  - Left atrium diameter greater than or equal to 50 mm by M-mode echocardiography
  - Left ventricular ejection fraction less than 0.40 by 2D-echocardiography
- Availability of one ECG within the last 6 months showing that the patient was or is in AF/AFL
- Availability of one ECG within the last 6 months showing that the patient was or is in sinus rhythm

The inclusion criteria were later modified to recruit patients that were older and had greater morbidity.

Table 6: Details of Study EFC5555 ATHENA

Design	Nr of subjects with age and sex	Duration of Treatment Reference therapy	Test Product Dosage Regimen Route of administration, Formulation	Results (efficacy)	Adverse Reactions
Multicentre, multinational, double blind, placebo controlled, parallel group of the efficacy of dronedarone for the prevention of cardiovascular hospitalisation or death from any cause in patients with AF/AFL	4628 enrolled, 4604 treated, 4626 completed  2459 males and 2169 females  50 Black, 4137 Caucasian, 441 other race  Age range 23 to 97 years   2291 in the dronedarone group, 2313 in the placebo group	12 months (up to 30 months: patients were treated from randomisation up to a common study end date)  Placebo tablets, twice daily, oral administration	Dronedarone 400 mg tablets; 400 mg twice daily, oral administration in the fed state  Randomisation and treatment allocation was by IVRS  Diltiazem, verapamil, beta blockers (except for sotalol) and digoxin could be co-administered	For the primary efficacy outcome variable, dronedarone was superior to placebo. The decrease in first cardiovascular hospitalization or death from any cause was apparent throughout the 30 month follow-up period. There was no significant difference between the treatment groups in death from any cause. The risk of cardiovascular hospitalisation was reduced in the dronedarone group. The risk of cardiovascular death was decreased in the dronedarone group.	TEAEs were reported in 1603 (69.3%) subjects in the placebo group and 1649 (72.0%) in the dronedarone  SAEs were reported in 489 (21.1%) subjects in the placebo group and 456 (19.9%) in the dronedarone  Deaths occurred in 65 (2.8%) subjects in the placebo group and 54 (2.4%) in the dronedarone.  Discontinuations because of TEAE occurred for 187 (8.1%) subjects in the placebo group and 290 (12.7%) in the dronedarone  Serum creatinine concentrations were increased by approximately 10 µmol/L and serum digoxin concentrations were increased by around 0.4 nmol/L in the dronedarone group.

The exclusion criteria included:

General:

- Any non-cardiovascular illness or disorder that could preclude participation or severely limit survival including cancer with metastasis and organ transplantation requiring immune suppression
- Pregnant women or women of childbearing potential not on adequate birth control
- Breastfeeding women

Criteria related to a cardiac condition:

- Patients in permanent atrial fibrillation
- Patients in unstable hemodynamic condition such as acute pulmonary edema within 12 hours prior to start of study medication; cardiogenic shock; treatment with intravenous pressor agents; patients on respirator; congestive heart failure of stage New York Heart Association (NYHA) IV within the last 4 weeks; uncorrected, haemodynamically significant primary obstructive valvular disease; haemodynamically significant obstructive cardiomyopathy; a cardiac operation or revascularization procedure within 4 weeks preceding randomization
- Planned major non-cardiac or cardiac surgery or procedures including surgery for valvular heart disease, coronary artery bypass graft, percutaneous coronary intervention, or on urgent cardiac transplantation list
- Acute myocarditis or constrictive pericarditis
- Bradycardia <50 beats per minute (bpm) and/or PR-interval  $\geq 0.28$  sec on the last 12-lead ECG
- Significant sinus node disease (documented pause of 3 seconds or more) or second or third degree atrioventricular (AV) block unless treated with a pacemaker

Criteria related to concomitant medications:

- Need of a concomitant medication that is prohibited in this trial, including the requirement for Vaughan-Williams Class I and III antiarrhythmic drugs, that would preclude the use of study drug during the planned study period

Criteria related to laboratory abnormalities:

- Plasma potassium <3.5 mmol/L (this must be corrected prior to randomization).
- A calculated glomerular filtration rate (GFR) at baseline <10 mL/min using the Cockcroft Gault formula

The study treatments are shown in Table 6.

The primary efficacy variable was the time from randomization to first occurrence of cardiovascular hospitalization or death from any cause, whichever was earlier, as assessed by the Investigator.

Secondary variables were time from randomization to:

- Death from any cause
- First cardiovascular hospitalization
- Cardiovascular death

Hypothesis tests were performed using the Log-rank test, Kaplan-Meier plots and Hazard Ratios using a Cox regression model.

For the primary efficacy outcome variable, dronedarone was superior to placebo. The decrease in first cardiovascular hospitalization or death from any cause was apparent throughout the 30 month follow-up period. The treatment difference was not influenced by baseline demographic characteristics or disease characteristics. There was no significant difference between the treatment groups in death from any cause. The risk of cardiovascular hospitalisation was reduced in the dronedarone group. The risk of cardiovascular death was decreased in the dronedarone group.

### **Efficacy Data from Comparator Controlled Trials**

A protocol for **Study EFC4968** was provided by the sponsor. No data were presented from this trial in the initial submission but details were provided in the supplementary data. **Study Efc4968 DIONYSOS** was a multinational, multicentre, randomised, double blind, double dummy, parallel group, comparator controlled clinical trial of dronedarone in comparison with amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation (Table 7). The study was sponsored by Sanofi-Aventis and conducted at 112 centres in 23 countries. The study appears to have been performed in an outpatient setting.

The inclusion criteria included:

- Subjects with documented AF for more than 72 hours for whom cardioversion and antiarrhythmic treatment were indicated in the opinion of the investigators and who were receiving anticoagulants

The exclusion criteria included:

- Subjects of either sex aged below 21 years
- Contraindication to oral anticoagulation
- Receipt of more than a total of twenty 200 mg tablets of amiodarone or more than 5 days intravenous amiodarone in the past
- Women of childbearing potential without adequate birth control, pregnant women and breastfeeding women
- Clinically relevant haematological, hepatic (ALT, AST > 1.5 X ULN), gastrointestinal, renal (serum creatinine >150 µmol/L), pulmonary, endocrinologic, psychiatric, neurological or dermatological disease

- Serum potassium <3.5 mmol/L and uncorrected or >5.5 mmol/L
- Unstable angina pectoris (ischaemic symptoms in the last 7 days) or recent myocardial infarction
- Documented AF episode motivating inclusion in the study after an acute condition known to cause AF (for example alcohol intake, thyrotoxicosis, acute infection, pericarditis, pulmonary embolism, cardiac surgery)
- History of torsades de pointes
- First degree family history of sudden cardiac death below age 50 years in the absence of coronary heart disease
- History of high degree AV block (second degree Mobitz 2 or higher), or significant sinus node disease (documented pause of 3 seconds or more) without a permanent pacemaker implanted
- Bradycardia <50 bpm on the last 12-lead ECG before randomisation
- Clinically overt CHF with NYHA Class III or IV at the time of randomisation
- Ongoing potentially dangerous symptoms when in AF such as angina pectoris, transient ischaemic attacks, stroke, or syncope
- Chronic AF defined as continuous AF for more than 12 months
- Wolff-Parkinson-White syndrome
- Patients with AFL
- Paroxysmal AF
- Long QT syndrome or QT- or QTc-interval  $\geq 500$  ms
- Treatment with other Class I or III antiarrhythmic drugs which could not be discontinued
- Hyperthyroidism
- Hypothyroidism
- Other contraindications to amiodarone including hypersensitivity to iodine

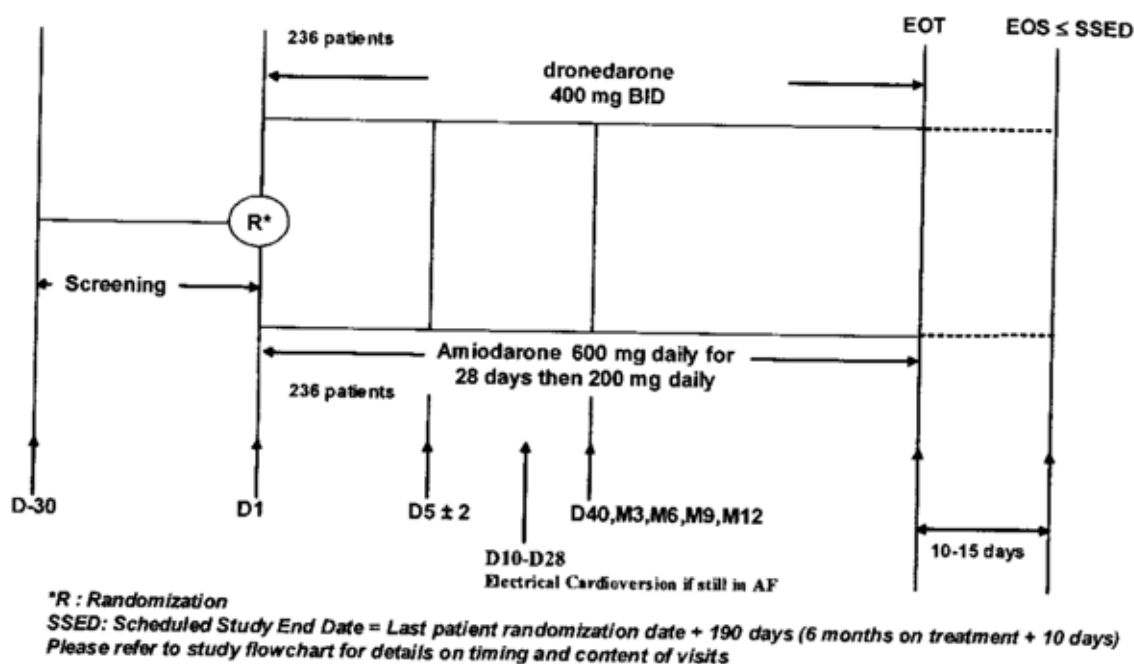
The study treatments are shown in Table 7.

The plan of the study design is displayed in Figure 2. Electrical cardioversion was to be performed if subjects were still in AF between Day 10 and Day 28. Subjects with unsuccessful electrical cardioversion were considered as having an AF recurrence at the date of the electrical cardioversion procedure. Recurrence of AF was documented from the time of first reversion to sinus rhythm. Spontaneous reversions to sinus rhythm and recurrence of AF were documented by 12-lead ECG.

Table 7: Details of Study Efc4968 DIONYSOS

Design	Nr of subjects with age and sex	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Results (efficacy)	Adverse Reactions
Multinational, multicentre, randomised, double blind, double dummy, parallel group, comparator controlled clinical trial of dronedarone in comparison with amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation	618 subjects were screened, 504 were randomised: 249 to dronedarone, 255 to amiodarone. 358 (71.0%) subjects were male, 146 (29.0%) female.  Age range 28 to 90 years.	At least 6 months  Subjects were treated for up to 13.8 months	Dronedarone 400 mg twice daily, orally with meals  Placebo for amiodarone  If still in AF, then electrical cardioversion between Day 10 and Day 28  Randomisation was stratified by study centre and used IVRS	Amiodarone 600 mg for 28 days then 200 mg daily, orally with meals  Placebo for dronedarone	More subjects in the dronedarone group discontinued treatment: 96 (36.6%) compared with 69 (27.1%) in the amiodarone. Discontinuation in the dronedarone group was primarily because of lack of efficacy: 53 (21.3%) subjects compared with 14 (5.5%) in the amiodarone. Fewer subjects in the dronedarone group discontinued because of AEs: 32 (12.9%) compared with 45 (17.6%) in the amiodarone.  Amiodarone was superior to dronedarone, HR (95% CI) dronedarone compare with amiodarone: 1.589 (1.275 to 1.98). AF recurrence was more frequent in the dronedarone group: 158 (63.5%) compared with 107 (42.0%).	The primary safety endpoint occurred in 83 (33.3%) subjects in the dronedarone group and 107 (42.0%) in the amiodarone. There was a higher rate of thyroid disorder, tremor and sleep disorder in the amiodarone group, and a higher risk of gastrointestinal events in the dronedarone group. AEs occurred in 151 (60.6%) subjects in the dronedarone group and 172 (67.5%) in the amiodarone. Bradycardia, sleep disorder, dizziness, headache, tremor, hypothyroidism and peripheral oedema were reported more frequently in the amiodarone group. There were 2 deaths in the dronedarone group and 5 for amiodarone. SAEs occurred in 34 (13.7%) subjects in the dronedarone group and 37 (14.5%) in the amiodarone. Discontinuation due to AE was more common in the amiodarone group: 45 (17.6%) subjects compared with 32 (12.9%) in the dronedarone.

Figure 2: Study design for Study Efc4968 DIONYSOS



The primary efficacy outcome measure was the composite endpoint of: either first recurrence of AF, and/or premature study drug discontinuation for intolerance (discontinuations due to an AE and all discontinuations not due to administrative reasons) or lack of efficacy. A 12-lead ECG was performed at each study visit: Screening, Day 1, Day 5, between Days 10 and 28, Day 40, Month 3, Month 5, Month 9, Month 12, end of treatment and end of study (10 days after end of treatment). There were no pre-specified secondary efficacy outcome measures. The primary safety outcome measure was defined as: the occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye or gastrointestinal specific events or premature drug discontinuation following any AE. This outcome measure appears to be defined according to the known adverse event profile of amiodarone. The secondary safety outcome measures were: AEs, ECG, vital signs and laboratory safety parameters (including thyroid function tests and INR). Serum biochemistry was performed at each study visit. INR was performed at each visit as required for patient management. TFTs were performed at screening, Day 1 and at each visit from Day 40.

The study was designed as a superiority comparison, with no provisions for a non-inferiority comparison. The primary analysis for comparison of the two treatment groups was a non-stratified 2-sided log-rank test with a level of significance of  $p < 0.05$ . Hypothesis tests were also performed using Kaplan-Meier estimation and 95% CI at each time point, and Hazard Ratios (95% CI) using Cox proportional hazards modelling. The efficacy and safety population included all randomised patients who received at least one dose of study treatment. The primary efficacy endpoint was analysed up to the last study drug intake plus 10 days.

The sample size calculation was based on the results of the SAFE-T study. Based on a recurrence rate of first AF/AFL with amiodarone of 34% at 6 months, a power of 80%, and an  $\alpha$  of 0.05, a sample size of 236 subjects in each group would be required to demonstrate a relative reduction in risk of 30%.

Amiodarone was superior to dronedarone. The Hazard Ratio (HR) (95% CI) with dronedarone compared with amiodarone for the primary efficacy outcome measure was 1.589 (1.275 to 1.98). A total of 184 (73.9%) subjects in the dronedarone group and 141 (55.3%) in the amiodarone had treatment failure. The Kaplan Meier estimate of median survival (treatment failure free) time was 41.0 (95% CI 37.0 to 45.0) days for dronedarone and 183.0 (99.0 to 275.0) days for amiodarone. As previously stated, there were no pre-specified secondary efficacy outcome measures. Hence, Hazard Ratios were not calculated and Kaplan Meier plots were not generated for the components of the primary efficacy outcome measure. However, the tabulated data show that AF recurrence was more frequent in the dronedarone group. Documented AF after cardioversion was more common in the dronedarone group: 91 (36.5%) subjects compared with 62 (24.3%) in the amiodarone. Unsuccessful cardioversion was more common in the dronedarone group: 29 (11.6%) subjects compared with 16 (6.3%) in the amiodarone. However, fewer subjects in the dronedarone group discontinued because of intolerance of study drug: 25 (10.0%) compared with 34 (13.3%) in the amiodarone.

#### *Evaluator's comments:*

Amiodarone was demonstrated to be superior to dronedarone for the composite endpoint of either first recurrence of AF, and/or premature study drug discontinuation for intolerance (discontinuations due to an AE and all discontinuations not due to administrative reasons) or lack of efficacy.

#### **Efficacy Data for Indications Not Sought in the Present Submission**

**Study ACT2771** was a multicentre, randomised, double blind, placebo controlled, parallel group study of the efficacy of IV dronedarone for the treatment of atrial fibrillation. The study included



patients with a sustained and well tolerated episode of AF of more than 12 hours and less than or equal to 48 hours duration. The study treatments were:

1. Dronedarone 1 mg/mL mannitol solution vials, 80 mg
2. Placebo

The treatments were administered as a single dose, infused intravenously over 60 minutes. The primary efficacy outcome measure was conversion to sinus rhythm at one, three and six hours after the start of the infusion (T1h, T3h and T6h). A total of 63 subjects were recruited, 61 were treated, and all 61 completed. There were 32 males and 29 females included in the study. The age range was 30 to 91 years. There were 31 subjects in the dronedarone group and 30 in the placebo. Six hours after the commencement of the infusion ten (32.3%) of 31 patients in the dronedarone group had converted, compared with four (13.3%) of 30 in the placebo group ( $p=0.079$ ).

**Study PDY2945** was an open label pilot study of intravenous dronedarone in suppressing ventricular tachycardia inducibility. The study included male or surgically sterile or post-menopausal females with a documented history of sustained ventricular tachycardia (VT), inducible during baseline programmed electrical stimulation (PES). Patients with an implantable cardioverter defibrillator (ICD) could be included if the other criteria were met and a PES indication existed. The study treatment was dronedarone 1 mg/mL mannitol solution vials, 80 mg as a single intravenous dose over 60 minutes. There was no comparator treatment. The primary efficacy outcome measure was induction of sustained VT through PES at T30 and T60, during a 60-minute infusion of 80 mg of dronedarone. Secondary endpoints were: change in VT characteristics in patients without suppression of VT inducibility; surface ECG and electrophysiological parameters during the electrophysiological study (EPS). Six subjects were recruited, and all six were treated and completed. There were five male and one female subject. The age range was 47 to 76 years. In one patient VT inducibility was suppressed at T30 and VF was induced at T60. All other patients were still inducible at T30 and T60; no sustained or non-sustained polymorphic VT were detected. Only minor changes in VT characteristics were observed after study drug infusion.

#### *Evaluator's comments*

The 400 mg twice daily dose was superior to placebo, dronedarone 600 mg twice daily and dronedarone 800 mg twice daily, as demonstrated by an increase in time to first AF recurrence and an increase in time to treatment failure, the primary clinical efficacy outcome measures (Study DRI3550 DAFNE). For secondary efficacy outcome measures, there was an increasing proportion of patients reverting without electrical cardioversion with increasing dronedarone dose and the ventricular rate in case of recurrence was lower in the dronedarone groups (Study DRI3550 DAFNE). Overall, there was no clinical advantage in increasing the dose beyond 400 mg twice daily.

In patients with AF, dronedarone decreased ventricular rate, and this decrease was maintained for at least 4 months (Study EFC4508 ERATO). Dronedarone decreased the risk of first recurrence on AF/AFL by 12 months by 22%, and also ventricular rate was reduced in the event of first recurrence (Study EFC3153 EURIDIS). The risk of AF/AFL recurrence was decreased by Day 30 of treatment and maintained over the 12 month follow-up period (Study EFC3153 EURIDIS, Study EFC4788 ADONIS). The risk of symptomatic first recurrence was also reduced over the 12-month follow up (Study EFC3153 EURIDIS, Study EFC4788 ADONIS). In Study EFC4788 ADONIS there was a decrease in the risk of recurrence of 11.7% at 12 months with dronedarone.

In patients with age  $\geq 70$  years, hypertension, diabetes, prior cerebrovascular accident or systemic embolism; and/or CHF there was a decrease in first cardiovascular hospitalization or death from any cause that was apparent throughout a 30 month follow-up period (Study EFC5555 ATHENA). The risk of cardiovascular hospitalisation was reduced in the dronedarone group and the risk of

cardiovascular death was decreased in the dronedarone group (Study EFC5555 ATHENA). However there was no difference in the risk of all-cause death (Study EFC5555 ATHENA).

There were no data from comparator controlled efficacy studies but a protocol for an ongoing study, Study EFC4968, was provided by the sponsor.

There were two studies conducted for a different route than that applied for under the present application. In a study of intravenous dronedarone for the conversion of AF/AFL to sinus rhythm there was no significant difference between the treatment groups, but the study appeared to be underpowered (Study ACT2771). In a study of VT inducibility in patients with ICD there was no significant effect for dronedarone (PDY2945).

Study DRI3550 DAFNE, Study EFC4508 ERATO, Study EFC3153 EURIDIS and Study EFC4788 ADONIS all excluded patients with clinically overt CHF. However, Study EFC5555 ATHENA included patients with CHF, but excluded those with NHYA grade IV. All of these studies were placebo controlled. Study DRI3550 DAFNE and Study EFC4508 ERATO were of 6 months duration. Study EFC3153 EURIDIS, Study EFC4788 ADONIS were of 12 months duration. Study EFC5555 ATHENA was for up to 30 months duration.

Therapeutic drug monitoring may be useful for improving dronedarone efficacy (Study EFC4788 ADONIS).

## Safety

### Data from Efficacy Studies.

For *Study DRI3550 DAFNE*, summarised in Table 2, the extent of exposure to study medication is summarised in Table 8.

Table 8: Total Duration of Treatment (in Days):

Treatment duration (days)	Statistics	Placebo N=66	800 mg N=76	1200 mg N=66	1600 mg N=62	p-value <sup>b</sup>
Total duration <sup>a</sup>	Mean	44.6	77.3	63.6	57.0	0.5387
	SD	61.1	79.2	76.0	71.0	
	Median	15.0	23.0	15.5	14.0	
	Minimum	4	4	2	1	
	Maximum	198	203	205	184	
	Missing	0	0	0	0	

a: Between the first and the last intake;

b: Jonckheere-Terpstra test

The number (%) of subjects with Treatment-Emergent Adverse Event (TEAEs) was similar for the four treatment groups: 56 (84.8%) for placebo; 41 (80.3%) for 400 mg; 57 (86.4%) for 600 mg and 53 (85.5%) for 800 mg. The pattern of TEAEs was similar for the four treatment groups (Table 9).

Table 9: Number (%) of Patients with Treatment-Emergent Adverse Event by Preferred Term with Incidence >2% in any Group

PREFERRED TERM	Placebo N=66 n (%)	800 mg N=76 n (%)	1200 mg N=66 n (%)	1600 mg N=62 n (%)	Dronedarone N=204 n (%)
Diarrhea	2 (3.0)	2 (2.6)	5 (7.6)	17 (27.4)	24 (11.8)
Tachycardia Supraventricular	5 (7.6)	10 (13.2)	5 (7.6)	5 (8.1)	20 (9.8)
Cardiac Failure	1 (1.5)	2 (2.6)	6 (9.1)	2 (3.2)	10 (4.9)
Palpitation	2 (3.0)	3 (3.9)	4 (6.1)	3 (4.8)	10 (4.9)
Abdominal Pain	0 (0.0)	5 (6.6)	2 (3.0)	2 (3.2)	9 (4.4)
Bradycardia	1 (1.5)	4 (5.3)	1 (1.5)	4 (6.5)	9 (4.4)
Headache	5 (7.6)	4 (5.3)	2 (3.0)	3 (4.8)	9 (4.4)
Nausea	3 (4.5)	1 (1.3)	2 (3.0)	5 (8.1)	8 (3.9)
Vertigo	0 (0.0)	3 (3.9)	3 (4.5)	2 (3.2)	8 (3.9)
Fatigue	1 (1.5)	2 (2.6)	3 (4.5)	2 (3.2)	7 (3.4)
Upper Respiratory Tract Infection	0 (0.0)	1 (1.3)	3 (4.5)	3 (4.8)	7 (3.4)
Dizziness	2 (3.0)	2 (2.6)	1 (1.5)	3 (4.8)	6 (2.9)
Bun Increased	1 (1.5)	1 (1.3)	2 (3.0)	2 (3.2)	5 (2.5)
Hypertension	3 (4.5)	3 (3.9)	1 (1.5)	1 (1.6)	5 (2.5)
Back Pain	1 (1.5)	3 (3.9)	0 (0.0)	1 (1.6)	4 (2.0)
Bronchitis	1 (1.5)	3 (3.9)	1 (1.5)	0 (0.0)	4 (2.0)
Chest Pain	3 (4.5)	1 (1.3)	1 (1.5)	2 (3.2)	4 (2.0)
Coughing	0 (0.0)	0 (0.0)	1 (1.5)	3 (4.8)	4 (2.0)
Hepatic Enzymes Increased	1 (1.5)	0 (0.0)	3 (4.5)	1 (1.6)	4 (2.0)
Sweating Increased	2 (3.0)	2 (2.6)	1 (1.5)	1 (1.6)	4 (2.0)
Dyspnoea	4 (6.1)	2 (2.6)	0 (0.0)	1 (1.6)	3 (1.5)
Inflicted Injury	2 (3.0)	2 (2.6)	0 (0.0)	1 (1.6)	3 (1.5)
Pharyngitis	0 (0.0)	1 (1.3)	0 (0.0)	2 (3.2)	3 (1.5)
QT Increased	0 (0.0)	0 (0.0)	1 (1.5)	2 (3.2)	3 (1.5)
Sleep Disorder	0 (0.0)	2 (2.6)	0 (0.0)	1 (1.6)	3 (1.5)
Vomiting	0 (0.0)	0 (0.0)	1 (1.5)	2 (3.2)	3 (1.5)
AV Block	2 (3.0)	0 (0.0)	1 (1.5)	1 (1.6)	2 (1.0)
Corneal Deposits	2 (3.0)	1 (1.3)	1 (1.5)	0 (0.0)	2 (1.0)
Dyspepsia	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)	2 (1.0)
Hypokalemia	1 (1.5)	0 (0.0)	2 (3.0)	0 (0.0)	2 (1.0)
Influenza-Like Symptoms	2 (3.0)	0 (0.0)	1 (1.5)	1 (1.6)	2 (1.0)
Constipation	3 (4.5)	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Renal Function Abnormal	2 (3.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Vision Abnormal	2 (3.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)

N = number of patients exposed, n = number of patients with at least one AE, % = percentage of patients

Treatment-emergent = from the first drug intake to 10 days after the last drug intake

There were similar numbers (%) discontinuing because of AEs: 40 (60.6%) for placebo; 36 (47.4%) for 400 mg; 40 (60.6%) for 600 mg and 38 (61.3%) for 800 mg. The commonest AE leading to discontinuation in the dronedarone groups was diarrhoea. Serious adverse effects (SAEs) were more frequent at the higher dronedarone doses: 4 (4.5%) for placebo; 2 (2.6%) for 400 mg; 5 (7.6%) for 600 mg and 7 (11.3%) for 800 mg. SAEs due to cardiac arrhythmia were more frequent in the higher dose dronedarone groups. There was one death: due to accidental trauma in the 800 mg group. More patients in the dronedarone groups had a decrease in haemoglobin, an increase in transaminases or increase in creatinine. There was a positive association between dronedarone trough plasma concentrations and QTc and an inverse relationship with heart rate.

For *Study EFC4508 ERATO*, summarised in Table 3, extent of exposure to study medication is summarised in Table 10.

Table 10. Summary of treatment exposure

	Placebo (N=89)	Dronedarone 800 mg (N=85)
N	89	85
Median	181	180
Mean	168.6	156.5
SD	40.7	57.9
Min - Max	2 - 238	7 - 211

PGM= SR33589/EFC4508/CSR/BS/PGM RPT/i5treatdurat.sas OUT= OUTPUT/I5 treatdurat.html (07MAR2005 - 19:14)

TEAEs were reported by 53 (59.6%) subjects in the placebo group and 65 (76.5%) in the dronedarone. The commonest TEAEs in the dronedarone group were nasopharyngitis, influenza and diarrhoea (Table 11).

Table 11. Number (%) of patients with Treatment Emergent Adverse Events for Preferred Terms with incidence &gt;2.0% in any treatment group

MedDRA Organ Class Preferred term	Placebo (N=89)		Dronedarone 800 mg (N=85)	
Infections and infestations				
Any event	22	(24.7%)	26	(30.6%)
Nasopharyngitis	9	(10.1%)	15	(17.6%)
Influenza	4	(4.5%)	8	(9.4%)
Bronchitis	2	(2.2%)	2	(2.4%)
Gastroenteritis	2	(2.2%)	0	(0%)
Gastrointestinal disorders				
Any event	12	(13.5%)	17	(20.0%)
Diarrhoea	1	(1.1%)	5	(5.9%)
Abdominal pain	1	(1.1%)	3	(3.5%)
Dyspepsia	0	(0%)	2	(2.4%)
Nausea	0	(0%)	2	(2.4%)
Flatulence	2	(2.2%)	0	(0%)
Respiratory, thoracic and mediastinal disorders				
Any event	6	(6.7%)	16	(18.8%)
Dyspnoea	2	(2.2%)	5	(5.9%)
Cough	1	(1.1%)	3	(3.5%)
Dyspnoea exertional	0	(0%)	3	(3.5%)
Chronic obstructive airways disease	0	(0%)	2	(2.4%)
Nervous system disorders				
Any event	11	(12.4%)	14	(16.5%)
Dizziness	4	(4.5%)	4	(4.7%)
Headache	3	(3.4%)	4	(4.7%)
Somnolence	0	(0%)	3	(3.5%)
General disorders and administration site conditions				
Any event	8	(9.0%)	10	(11.8%)
Fatigue	2	(2.2%)	4	(4.7%)
Non-cardiac chest pain	0	(0%)	3	(3.5%)
Malaise	0	(0%)	2	(2.4%)
Oedema peripheral	2	(2.2%)	1	(1.2%)
Chest pain	2	(2.2%)	0	(0%)
Cardiac disorders				
Any event	7	(7.9%)	8	(9.4%)
Palpitations	2	(2.2%)	2	(2.4%)
Cardiac failure	1	(1.1%)	2	(2.4%)
Bradycardia	0	(0%)	2	(2.4%)
Investigations				
Any event	4	(4.5%)	7	(8.2%)
Blood creatinine increased	0	(0%)	2	(2.4%)
Heart rate increased	2	(2.2%)	0	(0%)
Vascular disorders				
Any event	5	(5.6%)	5	(5.9%)
Hypertension	2	(2.2%)	1	(1.2%)
Musculoskeletal and connective tissue disorders				
Any event	4	(4.5%)	5	(5.9%)
Pain in extremity	1	(1.1%)	2	(2.4%)

Table 11 (cont)

MedDRA Organ Class Preferred term	Placebo (N=89)	Dronedarone 800 mg (N=85)
Skin and subcutaneous tissue disorders		
Any event	4 (4.5%)	5 (5.9%)
Rash	2 (2.2%)	1 (1.2%)
Hyperhidrosis	2 (2.2%)	0 (0%)
Metabolism and nutrition disorders		
Any event	4 (4.5%)	4 (4.7%)
Gout	1 (1.1%)	3 (3.5%)
Psychiatric disorders		
Any event	3 (3.4%)	4 (4.7%)
Anxiety	2 (2.2%)	1 (1.2%)
Injury, poisoning and procedural complications		
Any event	6 (6.7%)	3 (3.5%)
Contusion	3 (3.4%)	1 (1.2%)
Fall	2 (2.2%)	0 (0%)
Ear and labyrinth disorders		
Any event	0 (0%)	2 (2.4%)
Vertigo	0 (0%)	2 (2.4%)

Note: A patient can have AEs in more than one system organ class and in more than one preferred term

Serious adverse events (SAEs) were reported in 12 (13.5%) patients in the placebo group and 14 (16.5%) in the dronedarone group. There was one death during the study in the dronedarone group: sudden death in a patient with a history of congenital heart disease, and family history of sudden death and Steinert's disease. There were an additional two deaths (one in each treatment group) after study treatment had finished. Withdrawals due to TEAE occurred for nine (10.1%) patients in the placebo group and 13 (15.3%) in the dronedarone group. There was a mean increase in serum creatinine in the dronedarone group of 10.6 µmol/L. Digoxin levels increased by a mean of 41.4% in the dronedarone group. There was no apparent change in INR in the dronedarone group. Two patients in the placebo group and four in the dronedarone had elevations in AST >2xULN. Five patients in the placebo group and six in the dronedarone had elevations in ALT >2xULN. Decreases in heart rate and increases in QTc were more common in the dronedarone group.

For *Study EFC3153 EURIDIS*, summarized in Table 4, exposure to treatment is summarized in Table 12.

Table 12 Summary of treatment duration in days

	Placebo (N=201)	Dronedarone 800 mg (N=411)
n	201	411
Median	356	357
Mean	254.2	270.5
SD	138.0	134.4
Min - Max	3 - 377	1 - 420

PGM= SR33589/EFC3153/CSR/BS/PGM\_RPT/a5\_compl\_expos.sas OUT=i5\_treat\_durat (25OCT2004 - 11:27)

TEAEs were reported in 117 (58.2 %) subjects in the placebo group and 244 (59.4 %) in the dronedarone. The commonest TEAEs in the dronedarone group other than atrial fibrillation were diarrhoea, headache, influenza and nasopharyngitis (Table 13).

Table 13 Number (%) of patients with Treatment Emergent Adverse Events for the Preferred Terms with incidence >2.0% in either treatment group presented by System Organ Class

MedDRA Organ Class Preferred Term	Placebo (N=201)	Dronedarone 800 mg (N=411)
Cardiac disorders		
Any event	41 (20.4%)	72 (17.5%)
Atrial fibrillation	25 (12.4%)	34 (8.3%)
Bradycardia nos	5 (2.5%)	10 (2.4%)
Investigations		
Any event	23 (11.4%)	50 (12.2%)
Liver function test abnormal	4 (2.0%)	9 (2.2%)
Blood creatine phosphokinase increased	3 (1.5%)	9 (2.2%)
Gastrointestinal disorders		
Any event	23 (11.4%)	49 (11.9%)
Diarrhoea nos	7 (3.5%)	18 (4.4%)
Infections and infestations		
Any event	24 (11.9%)	47 (11.4%)
Influenza	7 (3.5%)	10 (2.4%)
Nasopharyngitis	6 (3.0%)	10 (2.4%)
Nervous system disorders		
Any event	22 (10.9%)	44 (10.7%)
Headache	10 (5.0%)	11 (2.7%)
Dizziness	2 (1.0%)	9 (2.2%)
Musculoskeletal and connective tissue disorders		
Any event	19 (9.5%)	35 (8.5%)
Back pain	3 (1.5%)	10 (2.4%)
General disorders and administration site conditions		
Any event	10 (5.0%)	33 (8.0%)
Oedema peripheral	7 (3.5%)	9 (2.2%)
Chest pain	1 (0.5%)	9 (2.2%)

Note: A patient can have AEs in more than one system organ class and in more than one preferred term

SAEs were reported in 53 (26.4 %) subjects in the placebo group and 76 (18.5 %) in the dronedarone group. There were two deaths during the study, both occurring in the dronedarone group: one sudden death; one myocardial infarction. Two further deaths occurred after study termination: one in the dronedarone group three months later from respiratory failure. Thirteen (6.5%) subjects in the placebo group and 35 (8.5%) in the dronedarone discontinued because of TEAEs. Serum creatinine increased by a mean of 8.8  $\mu\text{mol/L}$  from Day 7 in the dronedarone group. Elevations in liver enzymes occurred at a similar rate in both groups. Thyroid dysfunction occurred at a similar frequency in both treatment groups. Prolongation of the PR interval and prolongation of the QTc occurred more frequently in the dronedarone group.

For *Study EFC4788 ADONIS*, summarised in Table 5, the treatment exposure is summarized in Table 14.

Table 14: Summary of treatment duration in days - randomized and treated patients population

	<b>Placebo (N=208)</b>	<b>Dronedarone 800 mg (N=417)</b>
n	208	417
Median	328	356
Mean	224.1	255.9
SD	149.5	143.7
Min - Max	2 - 392	1 - 397

TEAEs were reported in 152 (73.1 %) subjects in the placebo group and 334 (80.1 %) in the dronedarone group (Table 15).

Excluding AF/AFL, TEAEs were reported in 149 (71.6 %) subjects in the placebo group and 326 (78.2 %) in the dronedarone group. Diarrhoea, nausea, vomiting, arthralgia, back pain and myalgia were more frequent in the dronedarone group. SAEs were reported in 47 (22.6 %) subjects in the placebo group and 88 (21.1 %) in the dronedarone group. Cardiac failure was reported as a SAE more commonly in the dronedarone group. Death occurred for three (1.4 %) subjects in the placebo group and six (1.4 %) in the dronedarone. The three deaths in the placebo group were due to: sudden death (1), cardiac arrest (1) and cerebrovascular accident (1). The six deaths in the dronedarone group were due to: sudden death (3, one of which was related to the study drug by the sponsor), congestive cardiac failure (1), third degree AV block (1), and metastatic neoplasm (1). The number (%) of subjects discontinuing because of TEAEs was 16 (7.7 %) in the placebo group and 45 (10.8 %) in the dronedarone group. Serum creatinine concentration increased in the dronedarone group by a mean of 11.9 µmol/L. Serum potassium concentration increased by a mean of 0.07 mmol/L at Day 7 in the dronedarone group. Disorders of thyroid function occurred to the same extent in both treatment groups. PR and QTc prolongation occurred to a greater extent in the dronedarone group than in the placebo group. Disorders of liver enzymes occurred at a similar rate for both treatment groups.

Table 15: Number (%) of patients with Treatment Emergent Adverse Events for the Preferred Terms with incidence >2.0% in either treatment group presented by System Organ Class

<b>MedDRA Organ Class Preferred Term</b>	<b>Placebo (N=208)</b>	<b>Dronedarone 800 mg (N=417)</b>
<b>Gastrointestinal disorders</b>		
Any event	50 (24.0%)	115 (27.6%)
Diarrhoea	13 ( 6.3%)	41 ( 9.8%)
Nausea	10 ( 4.8%)	28 ( 6.7%)
Vomiting	3 ( 1.4%)	14 ( 3.4%)
Abdominal pain	4 ( 1.9%)	11 ( 2.6%)
Abdominal pain upper	6 ( 2.9%)	10 ( 2.4%)
Dyspepsia	3 ( 1.4%)	9 ( 2.2%)
Constipation	7 ( 3.4%)	6 ( 1.4%)
<b>Infections and infestations</b>		
Any event	43 (20.7%)	106 (25.4%)
Upper respiratory tract infection	4 ( 1.9%)	24 ( 5.8%)
Nasopharyngitis	3 ( 1.4%)	12 ( 2.9%)
Urinary tract infection	1 ( 0.5%)	12 ( 2.9%)
Bronchitis	2 ( 1.0%)	11 ( 2.6%)
Sinusitis	3 ( 1.4%)	9 ( 2.2%)
Pneumonia	2 ( 1.0%)	9 ( 2.2%)
Influenza	5 ( 2.4%)	6 ( 1.4%)
<b>Musculoskeletal and connective tissue disorders</b>		
Any event	36 (17.3%)	85 (20.4%)
Arthralgia	6 ( 2.9%)	25 ( 6.0%)
Back pain	5 ( 2.4%)	18 ( 4.3%)
Pain in extremity	4 ( 1.9%)	15 ( 3.6%)
Myalgia	4 ( 1.9%)	10 ( 2.4%)
Joint swelling	1 ( 0.5%)	10 ( 2.4%)
Muscle cramp	4 ( 1.9%)	9 ( 2.2%)
<b>Nervous system disorders</b>		
Any event	41 (19.7%)	81 (19.4%)
Headache	20 ( 9.6%)	33 ( 7.9%)
Dizziness	8 ( 3.8%)	19 ( 4.6%)
<b>Cardiac disorders</b>		
Any event	40 (19.2%)	80 (19.2%)
Atrial fibrillation	16 ( 7.7%)	27 ( 6.5%)
Angina pectoris	6 ( 2.9%)	15 ( 3.6%)
Bradycardia	2 ( 1.0%)	11 ( 2.6%)
Cardiac failure	1 ( 0.5%)	9 ( 2.2%)
Cardiomegaly	6 ( 2.9%)	3 ( 0.7%)
<b>General disorders and administration site conditions</b>		
Any event	35 (16.8%)	80 (19.2%)
Oedema peripheral	13 ( 6.3%)	30 ( 7.2%)
Fatigue	11 ( 5.3%)	20 ( 4.8%)



Table 15 (cont):

MedDRA Organ Class Preferred Term	Placebo (N=208)	Dronedarone 800 mg (N=417)
Respiratory, thoracic and mediastinal disorders		
Any event	40 (19.2%)	75 (18.0%)
Dyspnoea	6 (2.9%)	13 (3.1%)
Epistaxis	2 (1.0%)	12 (2.9%)
Cough	5 (2.4%)	11 (2.6%)
Dyspnoea exacerbated	5 (2.4%)	4 (1.0%)
Pleural effusion	5 (2.4%)	2 (0.5%)
Investigations		
Any event	14 (6.7%)	75 (18.0%)
Blood creatinine increased	0 (0.0%)	16 (3.8%)
Skin and subcutaneous tissue disorders		
Any event	17 (8.2%)	55 (13.2%)
Rash erythematous	4 (1.9%)	9 (2.2%)
Injury, poisoning and procedural complications		
Any event	18 (8.7%)	38 (9.1%)
Fall	6 (2.9%)	3 (0.7%)
Psychiatric disorders		
Any event	11 (5.3%)	32 (7.7%)
Anxiety	1 (0.5%)	9 (2.2%)
Insomnia	5 (2.4%)	7 (1.7%)
Vascular disorders		
Any event	15 (7.2%)	29 (7.0%)
Hypertension	6 (2.9%)	13 (3.1%)

Note: A patient can have AEs in more than one system organ class and in more than one preferred term

For *Study Efc4968 DIONYSOS*, summarised in Table 6, the median (range) duration of exposure was 214 (2 to 415) days for dronedarone and 232 (4 to 415) days for amiodarone. There was no tabulation of duration of exposure to study treatment in the study report, but it appears that 84 subjects were exposed to dronedarone for 6 months and twelve for 12 months. It also appears that 126 subjects were exposed to amiodarone for 6 months and 13 for twelve months. The primary safety endpoint occurred in 83 (33.3%) subjects in the dronedarone group and 107 (42.0%) in the amiodarone. There was no statistically significant difference in the risk of primary safety outcome measure: HR (95% CI) dronedarone vs amiodarone 0.802 (0.602 to 1.068). There was a higher rate of thyroid disorder, tremor and sleep disorder in the amiodarone group, and a higher risk of gastrointestinal events in the dronedarone group (Table 16). The increase in the risk of gastrointestinal event in the dronedarone group was statistically significant: HR (95% CI) 1.982 (1.119 to 3.509), log-rank p-value 0.0166.

Table 16: Composition of the “First Main Safety Endpoint”, all randomized and treated subjects

First main safety endpoint	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg OD (N=255)
Number of patients with endpoint	83 (33.3%)	107 (42.0%)
Thyroid events	2 (0.8%)	15 (5.9%)
Hypothyroidism	2 (0.8%)	7 (2.7%)
Hyperthyroidism	0	3 (1.2%)
Thyroid function test abnormal (requiring medical intervention)	0	5 (2.0%)
Hepatic events	30 (12.0%)	27 (10.6%)
Liver enzymes (AST/ALT) increased	30 (12.0%)	27 (10.6%)
Neurological events	3 (1.2%)	17 (6.7%)
Tremor	0	5 (2.0%)
Sleep disorder	3 (1.2%)	12 (4.7%)
Skin events	2 (0.8%)	4 (1.6%)
Photosensitivity reaction (skin)	2 (0.8%)	4 (1.6%)
Eye events	1 (0.4%)	3 (1.2%)
Photophobia	0	2 (0.8%)
Vision blurred	1 (0.4%)	1 (0.4%)
Gastrointestinal events	32 (12.9%)	13 (5.1%)
Diarrhea	20 (8.0%)	5 (2.0%)
Nausea	10 (4.0%)	6 (2.4%)
Vomiting	2 (0.8%)	2 (0.8%)
Premature study drug discontinuation due to any AE	13 (5.2%)	28 (11.0%)

Note: First main safety endpoint is defined as the occurrence of the following treatment emergent event whichever comes first: thyroid, pulmonary, neurological, skin, eye or gastrointestinal specific events, or premature study drug discontinuation due to any AE, or liver enzymes (AST/ALT) above 2xULN and more than 0.5xULN from the baseline value.

On-treatment period is the period going from the first study drug intake to 10 days after the last study drug intake.

AEs were reported by 151 (60.6%) subjects in the dronedarone group and 172 (67.5%) in the amiodarone group (Table 17). Bradycardia, sleep disorder, dizziness, headache, tremor, hypothyroidism and peripheral oedema were reported more frequently in the amiodarone group. Bradyarrhythmia events were reported in 27 (10.6%) subjects in the amiodarone group and nine (3.6%) in the dronedarone. Haemorrhagic events were reported in 14 (5.6%) subjects in the dronedarone group and 29 (11.4%) in the amiodarone group: HR (95% CI) 0.504 (0.266 to 0.954) log-rank p=0.0318.

During treatment, there were two deaths in the dronedarone group: pulmonary embolism (1), unwitnessed death (1); and five deaths in the amiodarone group: CHF (1), septic shock (1), sudden death (1), sepsis due to treatment of lung cancer (1), and acute myocardial infarction (1). In the 10 day post-treatment follow-up period there were a further two deaths in the dronedarone group: thyroid cancer (1) and pancreatic carcinoma (1); and two deaths in the amiodarone group: lung cancer (1) and gastrointestinal haemorrhage (1).

SAEs were reported in 34 (13.7%) subjects in the dronedarone group and 37 (14.5%) in the amiodarone. The profiles of SAEs were similar for the two treatment groups.

Table 17: Number (%) of subjects with TEAEs for all Preferred Terms with an incidence of at least 2.0% in either treatment group presented by System Organ Class and Preferred Term, all randomized and treated subjects

<b>Primary System Organ Class Preferred Term</b>	<b>Dronedarone 400 mg BID (N=249)</b>	<b>Amiodarone 600 mg/200 mg OD (N=255)</b>
Any AE	151 (60.6%)	172 (67.5%)
Gastrointestinal disorders	54 (21.7%)	46 (18.0%)
Diarrhoea	23 (9.2%)	8 (3.1%)
Nausea	13 (5.2%)	9 (3.5%)
Abdominal pain upper	5 (2.0%)	5 (2.0%)
Constipation	2 (0.8%)	12 (4.7%)
Infections and infestations	37 (14.9%)	37 (14.5%)
Upper respiratory tract infection	7 (2.8%)	5 (2.0%)
Nasopharyngitis	6 (2.4%)	3 (1.2%)
Sinusitis	6 (2.4%)	2 (0.8%)
Bronchitis	4 (1.6%)	6 (2.4%)
Investigations	34 (13.7%)	37 (14.5%)
Transaminases increased	7 (2.8%)	0
Alanine aminotransferase increased	6 (2.4%)	2 (0.8%)
International normalised ratio increased	5 (2.0%)	9 (3.5%)
Hepatic enzyme increased	1 (0.4%)	6 (2.4%)
Thyroid function test abnormal	0	7 (2.7%)
Cardiac disorders	28 (11.2%)	42 (16.5%)
Cardiac failure	8 (3.2%)	1 (0.4%)
Bradycardia	5 (2.0%)	16 (6.3%)
Sinus bradycardia	3 (1.2%)	6 (2.4%)
Cardiac failure congestive	2 (0.8%)	6 (2.4%)
Respiratory, thoracic and mediastinal disorders	25 (10.0%)	21 (8.2%)
Dyspnoea	7 (2.8%)	5 (2.0%)
Cough	4 (1.6%)	7 (2.7%)

Table 17 (cont):

Primary System Organ Class Preferred Term	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg OD (N=255)
Nervous system disorders	20 (8.0%)	42 (16.5%)
Dizziness	8 (3.2%)	16 (6.3%)
Headache	4 (1.6%)	10 (3.9%)
Tremor	0	7 (2.7%)
General disorders and administration site conditions	15 (6.0%)	28 (11.0%)
Oedema peripheral	6 (2.4%)	13 (5.1%)
Fatigue	5 (2.0%)	5 (2.0%)
Vascular disorders	9 (3.6%)	23 (9.0%)
Hypertension	7 (2.8%)	16 (6.3%)
Injury, poisoning and procedural complications	9 (3.6%)	22 (8.6%)
Accidental overdose	2 (0.8%)	6 (2.4%)
Psychiatric disorders	6 (2.4%)	23 (9.0%)
Sleep disorder	3 (1.2%)	19 (7.5%)
Endocrine disorders	3 (1.2%)	14 (5.5%)
Hypothyroidism	3 (1.2%)	10 (3.9%)

Note: A patient can have AEs in more than one primary system organ class and in more than one preferred term

Study treatment discontinuation due to AE was more common in the amiodarone group: 45 (17.6%) subjects compared with 32 (12.9%) in the dronedarone group. The AEs leading to discontinuation that were more common in the amiodarone group were bradycardia, QT prolongation and sleep disturbance.

There was a decrease in mean heart rate in the dronedarone group relative to amiodarone, but this might just reflect the superior efficacy of amiodarone. There was also an increase in mean SRS interval and QTc in the amiodarone group relative to dronedarone, consistent with greater Type III antiarrhythmic effect. More patients in the amiodarone group had significant abnormalities in ECG post-baseline, but this is consistent with greater effects on electrical conduction in the heart.

Serum creatinine increased from baseline to Week 12 by a mean (SD) of 4.0 (15.4)  $\mu\text{mol/mL}$  in the dronedarone group and 8.1 (11.2)  $\mu\text{mol/L}$  in the amiodarone. Creatinine clearance decreased from baseline to Week 12 by a mean (SD) of 2.0 (12.0) mL/min in the dronedarone group and 8.5 (13.2) mL/min in the amiodarone. Marked elevations in AST or ALT were more common in the dronedarone group. Abnormalities in thyroid function tests were more common in the amiodarone group. At Day 10, INR was greater in the amiodarone group, mean (SD) 3.7 (1.6) compared with 2.8 (1.1) in the dronedarone group. There were no significant differences between the treatment groups in blood pressure or in other haematology parameters.

#### *Evaluator's comments:*

There were similar proportions of subjects with SAEs in the dronedarone and amiodarone treatment groups. However, overall there were fewer AEs in the dronedarone treatment group. Bradycardia, sleep disorder, dizziness, headache, tremor, hypothyroidism and peripheral oedema were reported more frequently in the amiodarone group. Abnormalities in thyroid function tests were more common in the amiodarone group. Haemorrhagic events were reported at a significantly higher rate in the amiodarone group and at Day 10, INR was greater in the amiodarone group. There were two

deaths in the dronedarone group and five in the amiodarone group. Serum creatinine increased to a greater extent in the amiodarone group than the dronedarone.

However, there was a significantly higher risk of gastrointestinal events in the dronedarone group and marked elevations in AST or ALT were more common in the dronedarone group.

For *Study EFC5555 ATHENA*, summarised in Table 7, exposure to study medication is summarised in Table 18.

Table 18 Summary of duration of treatment exposure - all randomized patients

	<b>Placebo (N=2327)</b>	<b>Dronedarone 400 mg BID (N=2301)</b>
Patient-years	3070.9	3031.4
Duration of exposure (days)		
n	2313	2291
Median	540	539
Mean	484.9	483.3
SD	248.5	253.6
Min - Max	1 - 916	1 - 907

TEAEs were reported in 1603 (69.3%) subjects in the placebo group and 1649 (72.0%) in the dronedarone (Table 19).

Diarrhoea, nausea, fatigue, bradycardia and elevated creatinine occurred more frequently in the dronedarone group. SAEs were reported in 489 (21.1%) subjects in the placebo group and 456 (19.9%) in the dronedarone group. Acute renal failure was more commonly reported in the dronedarone group. Deaths occurred in 65 (2.8%) subjects in the placebo group and 54 (2.4%) in the dronedarone group. The rate of non-cardiovascular death was higher in the dronedarone group but the rate of cardiovascular death was lower. Discontinuations because of TEAE occurred for 187 (8.1%) subjects in the placebo group and 290 (12.7%) in the dronedarone. Diarrhoea, nausea, fatigue and QT prolongation were more common reasons for withdrawal in the dronedarone group. Serum creatinine concentrations were increased by approximately 10 µmol/L and serum digoxin concentrations were increased by around 0.4 nmol/L in the dronedarone group. A similar proportion of patients had abnormalities in serum potassium. Diastolic blood pressure decreased by around 3 mmHg in the dronedarone group. Bradycardia, PR prolongation and QTc prolongation were more common in the dronedarone group.

Table 19: Number (%) of patients with treatment-emergent adverse events for all Organ Class and Preferred Term with incidence at least 2.0% during the on-treatment period

Primary System Organ Class Preferred term MedDRA (10.1)	Placebo (N= 2313)	Dronedarone 400 mg BID (N= 2291)
Any class - Any event	1603 ( 69.3 %)	1649 ( 72.0 %)
Gastrointestinal disorders	508 ( 22.0 %)	600 ( 26.2 %)
Diarrhoea	144 ( 6.2 %)	223 ( 9.7 %)
Nausea	72 ( 3.1 %)	122 ( 5.3 %)
Vomiting	27 ( 1.2 %)	49 ( 2.1 %)
Infections and infestations	582 ( 25.2 %)	542 ( 23.7 %)
Urinary tract infection	64 ( 2.8 %)	74 ( 3.2 %)
Upper respiratory tract infection	83 ( 3.6 %)	70 ( 3.1 %)
Nasopharyngitis	75 ( 3.2 %)	69 ( 3.0 %)
Bronchitis	72 ( 3.1 %)	67 ( 2.9 %)
Pneumonia	71 ( 3.1 %)	50 ( 2.2 %)
General disorders and administration site conditions	356 ( 15.4 %)	403 ( 17.6 %)
Oedema peripheral	119 ( 5.1 %)	147 ( 6.4 %)
Fatigue	90 ( 3.9 %)	115 ( 5.0 %)
Asthenia	47 ( 2.0 %)	68 ( 3.0 %)
Chest pain	55 ( 2.4 %)	52 ( 2.3 %)
Musculoskeletal and connective tissue disorders	396 ( 17.1 %)	381 ( 16.6 %)
Back pain	80 ( 3.5 %)	73 ( 3.2 %)
Arthralgia	62 ( 2.7 %)	64 ( 2.8 %)
Pain in extremity	44 ( 1.9 %)	50 ( 2.2 %)
Nervous system disorders	381 ( 16.5 %)	373 ( 16.3 %)
Dizziness	146 ( 6.3 %)	161 ( 7.0 %)
Headache	84 ( 3.6 %)	70 ( 3.1 %)
Respiratory, thoracic and mediastinal disorders	337 ( 14.6 %)	332 ( 14.5 %)
Dyspnoea	97 ( 4.2 %)	120 ( 5.2 %)
Cough	83 ( 3.6 %)	83 ( 3.6 %)
Investigations	206 ( 8.9 %)	308 ( 13.4 %)
Blood creatinine increased	31 ( 1.3 %)	108 ( 4.7 %)
International normalised ratio increased	47 ( 2.0 %)	48 ( 2.1 %)
Cardiac disorders	221 ( 9.6 %)	260 ( 11.3 %)
Bradycardia	28 ( 1.2 %)	81 ( 3.5 %)
Skin and subcutaneous tissue disorders	176 ( 7.6 %)	237 ( 10.3 %)
Rash	37 ( 1.6 %)	60 ( 2.6 %)
Injury, poisoning and procedural complications	227 ( 9.8 %)	219 ( 9.6 %)
Fall	70 ( 3.0 %)	69 ( 3.0 %)
Metabolism and nutrition disorders	203 ( 8.8 %)	186 ( 8.1 %)
Hypokalaemia	62 ( 2.7 %)	40 ( 1.7 %)
Vascular disorders	193 ( 8.3 %)	182 ( 7.9 %)
Hypertension	89 ( 3.8 %)	62 ( 2.7 %)
Renal and urinary disorders	118 ( 5.1 %)	116 ( 5.1 %)
Eye disorders	106 ( 4.6 %)	115 ( 5.0 %)
Psychiatric disorders	131 ( 5.7 %)	111 ( 4.8 %)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	118 ( 5.1 %)	105 ( 4.6 %)
Reproductive system and breast disorders	57 ( 2.5 %)	61 ( 2.7 %)
Ear and labyrinth disorders	70 ( 3.0 %)	56 ( 2.4 %)
Blood and lymphatic system disorders	65 ( 2.8 %)	47 ( 2.1 %)

Table 19 (cont):

Primary System Organ Class Preferred term MedDRA (10.1)	Placebo (N= 2313)	Dronedarone 400 mg BID (N= 2291)
Hepatobiliary disorders	38 ( 1.6 %)	44 ( 1.9 %)
Endocrine disorders	25 ( 1.1 %)	25 ( 1.1 %)
Surgical and medical procedures	18 ( 0.8 %)	22 ( 1.0 %)
Immune system disorders	16 ( 0.7 %)	12 ( 0.5 %)
Social circumstances	0 (0%)	2 (<0.1%)
Congenital, familial and genetic disorders	2 (<0.1%)	1 (<0.1%)

A patient can have AEs in more than one primary system organ class and in more than one preferred term

### Safety Data from Bioavailability Study Reports

In **Study 2397** there were 39 treatment emergent AEs, of which headache (11), phlebitis (4) and injection site reaction (4) were the most common. There was one SAE: injection site reaction. There were no deaths.

In **Study ALI3179**, there was one AE was reported: self-reverting bradycardia of short duration. There were no SAEs or deaths reported.

In **Study ALI3180**, three subjects reported AEs. One subject reported a SAE: fractured calcaneus. The other two AEs were: diarrhoea (1) and two episodes of non-sustained, asymptomatic ventricular tachycardia (1) (considered unrelated/unlikely by the investigator). There were no deaths.

### Safety Data from Comparative Bioavailability and Bioequivalence Study Reports

In **Study BDR2889**, 16 subjects experienced 34 treatment emergent AEs, the commonest being fatigue (4), dizziness (4) and nausea (3). Three were considered to be related to study drug: nausea (2) and postural hypotension (1). There were no SAEs or deaths reported during the study. One subject withdrew due to an AE: dizziness.

In **Study GAR3144**, five subjects reported eight TEAEs in the fasted group, the commonest AE being somnolence (3). Eight subjects reported 18 TEAEs in the fed group, the commonest being somnolence (3), headache (2), nausea (2), abdominal pain (2) and upper respiratory tract infection (URTI) (2). One subject discontinued because of an AE of URTI.

In **Study GAR3585**, there were four TEAEs reported in four subjects. There were no SAEs or deaths. One subject experienced two episodes of first degree AV block and one experience prolongation of QTc (451 ms from a baseline of 427 ms). There were no discontinuations due to AEs.

In **Study BDR4680**, one TEAE was reported: asthenia. There were no SAEs, deaths or discontinuations. Five subjects experienced an increase in QTc ranging from 30 to 38 ms. No QTc greater than 450 ms was reported.

In **Study TDU2163**, there were 26 TEAEs reported in 19 subjects. The most common AE was headache (9). Four subjects experienced dizziness (3) or orthostatic hypotension at doses of 500 mg or greater. There was a statistically significant dose-related decrease in AUC<sub>0-10h</sub> for systolic blood pressure (SBP) occurring from doses of 700 mg. The mean maximum decrease in SBP was 10 mmHg. There was no effect on heart rate, or diastolic blood pressure (DBP). PQ prolongation was seen at doses greater than 500 mg. There appeared to be an increase in QTc with dose but this was not statistically significant. One subject (400 mg dose) had 72 episodes of type II AV block (Wenkebach) on Holter monitor 5.5 hours after administration.

In **Study TDU2164**, there were 22 TEAEs. There was poor local tolerability: ten of 21 subjects experienced local reactions: burning sensations (3), veinitis (3), phlebitis (2) and vein irritation (2).

At the 80 mg dose two subjects had haematuria. There were no dose related changes in SBP, DBP, heart rate, P wave duration, QRS and QT intervals. There was a trend to increased PQ intervals and decreased T wave amplitude that were not statistically significant. Holter monitor recordings were performed that showed ventricular ectopic beats (VEBs) in many of the subjects post-dose but the investigator was not able to comment on whether the frequencies of these were increased or not. There were no SAEs, deaths or withdrawals reported during the study.

In **Study BEX2770**, there were ten TEAEs in three subjects in the oral dose group and 18 in four subjects in the intravenous group. The most frequent TEAE was headache (4). Elevations in gamma-glutamyl transferase (GGT) and AST of up to 2.5 x ULN were observed in three subjects. There were no SAEs, deaths or withdrawals.

In **Study TDU3007**, there were 26 TEAEs. The most common TEAE was injection site reaction (18). There were no SAEs, deaths or withdrawals due to AEs.

In **Study TDU4899**, PR prolongation and low degree AV block were observed in four of six subjects in the 1200 mg group. In all, ten subjects reported TEAEs: including nausea (3), and elevated bilirubin (3). There were no deaths, SAEs or withdrawals due to AEs.

In **Study TDR2395**, there were 35 TEAEs in 19 subjects. There was bradycardia during the exercise test, with the greatest effect with the 800 mg twice daily dosing. An increase in PR and QTc and decrease in T wave amplitude were seen at the higher doses. The commonest TEAEs were: dizziness: placebo (1), dronedarone (2); ventricular tachycardia: placebo (3), dronedarone (5); and AV block: placebo (2), dronedarone (5). There were three SAEs: all ventricular tachycardia: placebo (1), dronedarone (2). There were no deaths. Three subjects discontinued because of AEs (all of the subjects with SAEs).

In **Study LIN2890**, TEAEs were observed in twelve (70.6%) subjects in the 800 mg group, eight (47.1%) in the 200 mg and seven (41.2%) in the 400 mg. There was a higher frequency of AEs in the 800 mg dose group. The commonest TEAEs were: asthenia (12), headache (8) and myalgia (7). Two subjects withdrew because of AEs: urticaria (1) and myalgia (1). Two subjects in the 800 mg group experienced increases from baseline in QTc of >60 ms. There were no SAEs or deaths.

In **Study TDR3549**, TEAEs were reported in 26 subjects. The rate of TEAEs increased with increasing dose. Prolongation of PR and QT interval occurred in all dose groups, in addition to decreased amplitude of the T wave. The most frequent AE was AV block (16): first degree in 15 subjects and second degree in one. Non-sustained ventricular tachycardia occurred in five subjects on dronedarone and four on placebo. Three subjects (one on 1400 mg and two on 1600 mg) had QTc prolongation >450 ms. One subject in the 1200 mg group had elevated transaminases (ALT, AST and GGT). Two subjects had elevated potassium, two subjects had elevated glucose, and one had a mild elevation in bilirubin. There were no deaths or SAEs. There was one discontinuation due to an AE.

In **Study TDR2394**, there were eleven TEAEs reported in nine subjects: the commonest AE was headache (4). Two subjects had elevations in hepatic transaminases. There were no SAEs and no deaths reported during the study. There were no discontinuations because of AEs. T3 and T4 were significantly decreased in some of the dosing groups but TSH was not affected. PQ interval increased in a dose dependent manner. There was no significant effect upon QRS or QTc at individual time points. There was no statistically significant effect upon PVBs.

In **Study POP2769**, four subjects reported five TEAEs after the single dose administration, and 20 TEAEs were reported in 14 subjects during the repeated administration phase. The commonest TEAEs after dronedarone were: asymptomatic non-sustained VT (5), diarrhoea (3) and second degree AV block (2). There was a significant increase in mean PR interval of 9 ms in the elderly male group. Mean QTc increased by 27.6 ms for the group as a whole. Six subjects discontinued



due to AEs: four on dronedarone due to VT (2), AF (1) and sinus bradycardia (1); and two on placebo due to VT (2). There were no SAEs or deaths.

In **Study POP2896**, two (of three) subjects reported AEs. The healthy volunteer reported loose stools. One of the hepatic impaired subjects reported toothache, insomnia and two episodes of convulsions. The convulsions were reported as an SAE and led to discontinuation. There were no deaths.

In **Study POP5820**, there were 16 patients with TEAEs. TEAEs were more frequent in the hepatic impaired patients and on the 400 mg twice daily dosing. There were no deaths or SAEs. One subject discontinued due to an AE which consisted of blurred vision, hyperhydrosis, tremor, asthenia, dry mouth and headache. QTc >450 ms (males) and >470 ms (females) occurred in seven of nine patients with hepatic impairment on the 400 mg twice daily dosing compared with none in the healthy subjects.

In **Study PDY5850**, TEAEs were reported in eight (38.1%) subjects in the dronedarone group and five (41.7%) subjects in the placebo. Plasma creatinine was increased in the dronedarone group, with a more marked increase in the moderate renal impairment group. Plasma renin activity and plasma urea were also increased in the dronedarone group. There was no difference between dronedarone and placebo in plasma N-methylnicotinamide, urea, aldosterone, angiotensin II and cortisol concentration from Day 1 to Day 14. QTc >450 ms were recorded in six subjects in the dronedarone group, and there were two subjects in the placebo and two in the dronedarone with increase in QTc from baseline of >60 ms. There were no SAEs, deaths or discontinuations due to TEAEs.

In **Study INT2631**, six subjects experienced TEAEs. The commonest TEAE was headache (2). There were no clinically relevant changes in vital signs or laboratory safety parameters. There was one SAE: one subject discontinued because of an increase in INR in the warfarin only phase. There were no deaths reported.

In **Study INT2634**, there were six TEAEs in four subjects. There were no SAEs or deaths reported. One subject discontinued because of an intercurrent illness. There were no significant effects on ECG parameters of dronedarone and digoxin in combination.

In **Study INT2636**, five subjects reported TEAEs. The commonest TEAE was ventricular tachycardia (2). There were no SAEs. There were no deaths. Three subjects discontinued because of AEs: first degree AV block on dronedarone alone (1), self resolving ventricular tachycardia on dronedarone plus propranolol (1) and second degree Wenckebach type AV block on dronedarone plus propranolol. There was a significant interaction effect between propranolol and dronedarone on PQ and QTc. There were no clinically relevant changes in biochemistry.

In **Study INT2931**, there were seven TEAEs reported in four subjects. There were no SAE or deaths. There were no clinically significant changes in vital signs, ECG findings or laboratory tests.

In **Study INT3353**, there were four TEAEs were reported in four subjects: asymptomatic non-sustained ventricular tachycardia (2), second degree AV block (1) and headache (1). There were no AEs and no deaths. There was one withdrawal due to an AE: asymptomatic non-sustained ventricular tachycardia.

In **Study INT3560**, there were four of 18 subjects that reported TEAEs during dronedarone alone compared with ten of 17 during dronedarone in combination with pantoprazole. The commonest AEs was headache (8) followed by flatulence (4). There were no SAEs or deaths. One subject withdrew because of urticaria. There were no clinically relevant laboratory, ECG or vital sign abnormalities.

In **Study INT3561**, there was a statistically significant increase in PR interval with ketoconazole co-administration of, mean (SEM) 13.0 (3.5) ms,  $p=0.0006$ . With ketoconazole co-administration, there was a mean (SEM) increase in QTc of 3.9 (1.7) ms,  $p=0.0488$ . There was one TEAE during dronedarone administration. There were no SAEs, deaths or withdrawals. There were no laboratory adverse events.

In **Study INT3683**, there were 37 TEAEs: 13 on dronedarone alone, 13 on rifampicin alone and eleven on rifampicin and dronedarone. There were no SAEs or deaths. One patient discontinued due to an AE: nausea and vomiting. There were no clinically relevant laboratory adverse events. The PR interval was decreased with rifampicin co-administration indicating decreased dronedarone effect.

In **Study PDY3828**, four (66.7%) subjects reported TEAEs in the 800 mg group, eight (88.9%) in the 1200 mg group and 18 (90%) in the 1600 mg group. In the dronedarone treated groups, the commonest AE was bradycardia (13). There were no SAEs or deaths. Four subjects discontinued because of AEs: three of which were heart rate and rhythm disorders, and one of which was a rash. There was a statistically significant decrease in the mean velocity of endocardial circumferential fibre shortening  $V_{cf_{mean}}$ , with metoprolol and dronedarone co-administration indicating a reduction in myocardial contractility.

In **Study INT4074**, TEAEs were reported in eleven subjects. The commonest TEAEs were diarrhoea (3) and AV block (3). There were no SAEs, deaths or discontinuations due to TEAEs. There was a statistically significant increase in PR interval when dronedarone was co-administered with diltiazem: 14.37 ms ( $p=0.0001$ ), also for QT-interval: 5.79 ms ( $p=0.0003$ ) and for QTc interval: 3.80 ms ( $p=0.0002$ ). At the 1600 mg dronedarone dose, there was a significant increase in mean QRS of 1.78 ms ( $p=0.0118$ ). Conversely, there was a decrease in QT interval with dronedarone and nifedipine co-administration of 4.39 ms ( $p=0.0283$ ). Two subjects had elevated blood eosinophils and one had reduced neutrophils; none of which were clinically significant.

In **Study INT4442**, TEAEs were reported in 14 subjects. The commonest TEAEs with dronedarone alone were diarrhoea (12), headache (8) and dizziness (5). There were no deaths or SAEs. One subject withdrew due to a TEAE: first degree AV block. There were no significant laboratory test abnormalities.

In **Study INT4695**, twelve subjects reported TEAEs during dronedarone treatment. The commonest TEAEs were: diarrhoea (7) and headache (3). There were no deaths or SAEs reported during the study. Two subjects reported AV block during dronedarone treatment. There were two withdrawals due to TEAEs: headache (1) and first degree AV block (1). One subject was reported as having hyperkalaemia.

In **Study INT4880**, four (16.7%) subjects reported TEAEs on dronedarone alone, four (16.7%) on co-administration and five (20.8%) on simvastatin alone. There were no SAEs or deaths reported during the study. One subject withdrew because of a TEAE: skin rash. There were no clinically significant laboratory or ECG abnormalities.

In **Study INT4881**, TEAEs were reported by 11 (40.7%) subjects on dronedarone alone, 12 (42.9%) subjects on nisoldipine alone and 21 (77.8%) subjects during co-administration. Palpitations were more commonly reported during co-administration (6), compared with dronedarone (1) and nisoldipine (1). Headache was the most common TEAE: co-administration (16), dronedarone (4) and nisoldipine (10). There were no SAEs or deaths during the study. One subject withdrew because of a TEAE: mild elevation of liver enzymes during nisoldipine. There were two patients with elevations in liver enzymes, reported as TEAEs which were not considered clinically significant. There were no clinically significant changes in vital signs or ECG parameters.

In **Study INT4882**, TEAEs were reported by four (21.1%) subjects during dronedarone alone, two (10.5%) during verapamil alone and one (5.6%) during co-administration. There were no SAEs or deaths. There was one withdrawal due to a TEAE: maculopapular rash during verapamil alone. There were no treatment emergent abnormalities in laboratory parameters. There were no reports of QTc>500 ms, but two subjects in the dronedarone only, one in the verapamil only and nine in the co-administration group had a QTc reported as >450 ms. PR and QT<sub>C</sub> were increased in co-administration relative to either dronedarone or verapamil as monotherapy.

In **Study INT4884**, TEAEs were reported by 20 (71.4%) subjects on dronedarone, 18 (62.1%) on losartan and 23 (85.2%) on co-administration. The commonest TEAE was headache: dronedarone (8), losartan (7) and co-administration (8). There were no SAEs, deaths or withdrawals due to TEAEs. There were no clinically significant abnormalities in laboratory tests. There was no increase in ECG changes with co-administration.

In **Study INT4886**, TEAEs were reported in five subjects during dronedarone and grapefruit juice and three during dronedarone alone. There was one SAE: AV block. There were two discontinuations due to a TEAE: the AV block recoded as an SAE; and another subject had abnormal liver function tests. There were no deaths reported during the study. There were five reports of PR >220 ms and three of QTc>450 ms. There were no reports of QTc>500 ms.

In **Study INT5084**, TEAEs were reported in 23 (63.9%) subjects during theophylline alone and 22 (59.5%) during co-administration. This difference in rate of TEAEs may reflect the decrease in theophylline plasma concentrations. There were no SAEs or deaths. Three subjects discontinued because of TEAEs: two during co-administration because of gastrointestinal TEAEs. In addition, five subjects discontinued during theophylline alone because of high plasma concentrations of theophylline. QTc values >450 ms were observed in five subjects during theophylline alone and ten during co-administration.

In **Study INT5139**, TEAEs were reported in six (31.6%) subjects in the digoxin alone group and four (20.0%) in the co-administration group. There were no SAEs or deaths reported during the study. There was one discontinuation because of tonsillitis. There were no clinically significant abnormalities in laboratory tests. Increase from baseline in QTc was more pronounced in the co-administration group.

### **Safety Data from Pharmacodynamic Studies**

In **Study PDY5487**, there were nine subjects with TEAEs during dronedarone treatment and four during placebo. The most common TEAE in the dronedarone group was headache (5). There were no SAEs or deaths. There were no discontinuations. No clinically significant abnormalities in laboratory findings or ECG were reported.

In **Study PDY5923**, TEAEs were reported in eight (38.1%) subjects in the dronedarone group and two (20%) in the placebo. The most commonly reported TEAE in the dronedarone group was “flu-like illness”. There were no SAEs or deaths reported during the study. There were no withdrawals due to TEAEs. One subject in the dronedarone group had a fall in haemoglobin  $\geq 2$  g/L. There were no clinically significant changes in ECG reported.

In **Study PDY2399**, nine TEAEs were reported in eight patients. Four episodes of AF were reported in three patients. There were no SAEs or deaths reported during the study. No patients discontinued due to TEAEs. Elevated serum potassium was noted in three dronedarone treated patients and one amiodarone treated patient. Ten patients had blood glucose values higher than the reference range at some point during the study.

In **Study PDY2400**, there were 42 TEAEs reported in 17 patients. The commonest TEAEs were: chest pain (7) and back pain (5). There was one SAE resulting in death: cardiac arrest with

ventricular fibrillation which resulted in death. The SAE/death was not attributed to the study drug but to the patient's disease state.

In **Study ACT2401**, TEAEs were reported in 29 (72.5%) patients in the placebo group, 16 (55.2%) in the 400 mg, 21 (70.0%) in the 800 mg and 15 (60%) in the 1200 mg. The commonest TEAEs in the dronedarone groups were: chest pain (10), dizziness (7), fatigue (6), and cardiac failure (6). SAEs were reported in three patients in the placebo group, two in the 400 mg, three in the 800 mg and two in the 1200 mg. Discontinuations due to TEAEs occurred in one patient in the placebo group, one in the 400 mg, two in the 800 mg and three in the 1200 mg. There were three discontinuations due to prolonged QT intervals. Three deaths were reported: one during treatment in the 1200 mg group (sudden unexplained; relationship to study drug reported as unknown); two after completion (both due to cardiac failure). One patient had an elevated ALT, and one had a marked decrease in T3.

In **Study PDY2402**, 20 TEAEs were reported in eight subjects. Ten SAEs were reported in six subjects: ventricular tachycardia (7), ventricular fibrillation (3). There were no deaths or withdrawals due to TEAEs. One subject had elevated GGT. One subject in the 400 mg group developed a QTc greater than 450 ms (550 ms on Day 28). On Holter monitor nine subjects developed non-sustained VT: two in the amiodarone group; three in the 400 mg dronedarone group and four in the 800 mg.

### **Safety Data from Pooled Analyses**

**Report APS-AF-AFL** provides a pooled analysis of safety data in subjects with AF/AFL. The report provides a tabulation of all TEAEs reported during the development for the indication of AF/AFL. The report identifies possible associations of dronedarone with renal failure, drug toxicity, photosensitivity, skin infection, increased levels of cardioactive drug, dysgeusia, coronary artery stenosis, neuralgia and restless legs syndrome. Overall, the pattern of SAEs was similar for dronedarone and placebo. Diarrhoea, nausea and vomiting were important treatment limiting adverse events. The report did not indicate an increased risk of pulmonary, hepatobiliary, haematological or ocular disorders. Unfortunately the report did not contain a summary or an analysis of patient exposure to study medication.

**Report APS-HS** provides a pooled analysis of safety data from studies that enrolled healthy volunteers. The data presented were a complete listing of all TEAEs, SAEs and TEAEs resulting in discontinuation. The commonest TEAEs were headache, dizziness and bradycardia. The data presented were consistent with that presented for the individual studies. The analysis of the pooled data did not identify any new safety signals.

### **Additional Safety Data from Studies Conducted in Support of Alternative Indications and/or Formulations**

For **Study ACT2771**, TEAEs were reported in 15 (48%) subjects in the dronedarone group and 12 (40%) in the placebo. The commonest TEAE in the dronedarone group was injection site pain and inflammation (13). There were no deaths during the study. There were five SAEs: two in the placebo group and three in the dronedarone. AF was reported as a SAE in two subjects in both the placebo and dronedarone groups. Cardiac failure was reported as a SAE in one patient in the dronedarone group. There were no clinically significant abnormalities in laboratory tests.

In **Study PDY2945**, 15 TEAEs were reported in the six subjects. There were four SAEs: atrial fibrillation (1), ventricular fibrillation (1), ventricular tachycardia (1), and pneumothorax (1). There were no deaths and no withdrawals.

**Study DRI3151** was a multicentre, double blind, randomised placebo controlled trial of the safety and tolerability of dronedarone in patients with implantable cardioverter defibrillator (ICD). The

study included patients with an ICD and an indication or potential indication for adjunctive anti-arrhythmic therapy; Left ventricular ejection fraction (LVEF)  $\geq 40\%$ ; history of coronary artery disease and/or dilated cardiomyopathy; and an ICD with electrogram documentation capabilities. The study treatments were: dronedarone 200 mg tablets: 600 mg, 800 mg or 1000 mg; twice daily, oral administration in the fed state. The comparator was placebo tablets. The treatment duration was 30 days. A total of 76 patients were recruited, 73 were treated, and 47 completed. There were 69 males, and seven females. The age range was 35 to 84 years. Fifty four patients received dronedarone and 19 received placebo. TEAEs were reported in 45 (83%) subjects in the dronedarone group and 13 (68.4%) in the placebo. Diarrhoea, dizziness and dyspnoea were the most commonly reported TEAEs in the dronedarone group. SAEs were reported in 17 (31.5%) subjects in the dronedarone group and two (10.5%) in the placebo. Discontinuation because of TEAE occurred for 15 (27.8%) subjects in the dronedarone group and three (15.8%) placebo patients. There was one death (sudden death) in a subject in the 1000 mg group, judged by the Investigator to be possibly related to the study treatment. Elevations in AST and ALT occurred in 5 (9.6%) subjects in the dronedarone group and none in the placebo.

**Study LTS3841** was a multicentre, double blind, randomised, placebo controlled long-term follow up for Study DRI3151. The study included patients with an ICD who had been included in Study DRI3151. The study treatments were: dronedarone 200 mg tablets; 600 mg, 800 mg or 1000 mg, twice daily oral administration. The comparator was placebo. Treatment duration was for 6 months. The outcome measures were the incidence of serious and non-serious adverse events (AEs); and based on ICD recordings, incidence of appropriate intervention and inappropriate shocks; the incidence of non-sustained ventricular arrhythmias (from 24-hour Holter); and changes in ventricular pacing threshold parameters. There were 73 patients enrolled in the study, 40 were treated and 27 completed. There were 37 males and three females. The age range was 35 to 84 years. Fifteen subjects were included in the 600 mg group, nine in the 800 mg, four in the 1000 mg, and twelve in the placebo. Fewer dronedarone patients had appropriate ICD interventions (from 22.2% to 53.3% of dronedarone patients, versus 66.7% of placebo patients:  $p=0.0331$ ). Inappropriate post-baseline shocks were observed in one (8.3%) placebo patient and three (20%) patients in the 1200 mg dronedarone group. No clinically relevant differences among groups in magnitude of changes in pacing threshold parameters were observed.

TEAEs were reported in 28 (100%) subjects in the dronedarone group and 11 (91.7%) in the placebo group. Diarrhoea, dizziness and dyspnoea were the most frequently reported TEAEs in the dronedarone group. Three dronedarone subjects had elevations of AST and/or ALT. There were no deaths in the extension study. SAEs were reported in 14 (50%) dronedarone subjects and four (33.3%) placebo. Six (21.4%) subjects in the dronedarone group discontinued because of TEAEs, and two (16.7%) in the placebo.

**Study EFC4966 ANDROMEDA** was a multicentre, double blind, parallel-group, randomised, placebo controlled trial of dronedarone for reduced death from any cause, or hospitalisations for worsening heart failure in patients with congestive heart failure. The study was terminated early and the following statement included in the report:

“On 16 January 2003, 7 months after randomization of first patient, the inclusions in the study and ongoing study drug treatment were discontinued following a recommendation of the DSMB, because of a higher number of deaths observed in patients randomized to the active treatment compared to placebo. Following a second safety analysis (17 February 2003) the DSMB recommended follow-up of mortality, major clinical events and renal function for all patients, up to 17 July 2003 (6 months after end of inclusions).”

The study treatments were:

1. Dronedarone 400 mg tablets; 400 mg twice daily, oral administration in the fed state

## 2. Placebo

Treatment was for 12 months duration.

The primary endpoint was: death from any cause or hospitalization for worsening heart failure. The secondary endpoints were:

- death from any cause;
- adjudicated hospitalization for worsening heart failure;
- adjudicated hospitalization for acute cardiovascular reasons;
- adjudicated arrhythmic/sudden death;
- atrial fibrillation/atrial flutter (AF/AFL) occurrence

A total of 653 subjects were enrolled in the study, 627 were treated, and 483 completed. There were 472 males, and 155 females. The age range was 27 to 96 years. There were 310 subjects in the dronedarone group and 317 in the placebo. The mean extent of exposure in the 627 patients evaluated for safety was 62.1 days in dronedarone patients and 63.6 days in placebo patients. A higher proportion of subjects in the dronedarone group prematurely withdrew from the study. All subjects from Centre 616004 were excluded from analysis because of protocol deviations.

The treatment groups were similar in baseline demographic characteristics. There was a similar proportion of subjects in each group with AF/AFL at baseline, although there were some between group differences in the type of AF/AFL. A higher proportion of patients in the dronedarone group had a history of ischaemic heart disease, coronary bypass grafting, hypertension, alcohol induced cardiomyopathy and diabetes mellitus. Severity of congestive cardiac failure was similar at baseline. Concomitant medication was similar for both groups during the trial.

The risk of death was greater in the dronedarone group (25 deaths) than the placebo (12 deaths); Relative Risk (95% CI) 2.13 (1.071 to 4.274), Log-rank  $p=0.02717$ . Cardiovascular death occurred in 24 (96%) subjects in the dronedarone group and nine (75%) subjects in the placebo. Absence of treatment with ACEI or angiotensin II receptor antagonist was a covariate risk factor for death. Baseline creatinine clearance  $<50$  mL/min; congestive heart failure more severe than NYHA Class II; and digitalis co-administration were also covariate risk factors for death. There was no statistically significant difference between groups in first hospitalization for worsening heart failure. First hospitalization for heart failure was more frequent in the dronedarone group (71 subjects) than the placebo (50 subjects),  $p=0.02448$ . There was no significant difference between the groups in the number of conversions among patients with AF/AFL at baseline and the number of AF/AFL occurrences.

TEAEs were reported in 221 (69.7 %) subjects in the placebo group, and 230 (74.2 %) in the dronedarone. Cardiac failure, diarrhea, cough and hypotension occurred more frequently in the dronedarone group. SAEs were reported in 121 (38.2 %) subjects in the placebo group and 131 (42.3 %) in the dronedarone. The commonest SAE in the dronedarone group was cardiac failure. Death occurred in 13 (4.1 %) subjects in the placebo group and 24 (7.7 %) in the dronedarone, as discussed above. Discontinuations because of TEAEs occurred for 28 (8.8%) subjects in the placebo group and 57 (18.4%) in the dronedarone group. The commonest TEAE leading to discontinuation in the dronedarone group was cardiac failure. Bradycardia, prolongation of the PR interval and QT prolongation were more commonly reported in the dronedarone group.

### *Evaluator's comments*

Dronedarone was associated with an increased risk of TEAEs in comparison with placebo. There was an increased risk of nausea, vomiting and diarrhoea that was consistent across the clinical studies. Dronedarone was consistently associated with prolongation of the PR and QTc intervals. There are possible associations of dronedarone with: renal failure, drug toxicity, photosensitivity,

skin infection, increased levels of cardioactive drug, dysgeusia, coronary artery stenosis, neuralgia, restless legs syndrome (Report APS-AF-AFL). Diarrhoea, nausea and vomiting are important treatment limiting adverse events (Report APS-AF-AFL).

Except for Study EFC5555 ATHENA there appeared to be an increased risk of sudden and/or cardiovascular death. In subjects with CHF, Study EFC4966 indicated an increased risk of cardiac death and for first hospitalization with CHF. This may have been related to an imbalance of treatment with ACE inhibitors or angiotensin II receptor antagonists.

However, the data did not indicate an increased risk of pulmonary, hepatobiliary, haematological or ocular disorders (Report APS-AF-AFL). This might invite favourable comparisons with amiodarone, but it should be noted that because of the absence of comparator controlled trials such conclusions are limited.

A number of drug interactions were identified by the safety data. There was a significant interaction effect between propranolol and dronedarone on PQ and QTc (Study INT2636). There was a statistically significant decrease in myocardial contractility with the combination of metoprolol and dronedarone (Study PDY3828). There was a statistically significant increase in PR interval when dronedarone was co-administered with diltiazem (Study INT4074). There was a decrease in QT interval with dronedarone and nifedipine co-administration (Study INT4074). PR and QTC was increased in co-administration relative to either dronedarone or verapamil as monotherapy (Study INT4882). QTc values >450 ms were observed in five subjects during theophylline alone and ten during co-administration (Study INT5084). Increase from baseline in QTc was more pronounced with the combination of digoxin and dronedarone (Study INT5139).

## **Clinical Summary and Conclusions**

### **Pharmacodynamics**

Renal effects: The tubular organic cation transporter (OCT) is inhibited by dronedarone. There was a 15% increase in plasma creatinine in the dronedarone group compared to placebo.

Cardiovascular effects: There was a dose related decrease in pulmonary vascular resistance in the dronedarone groups, a decrease in heart rate and a slight increase in QT interval in the dronedarone 20 mg group. Intravenous dronedarone resulted in a decrease in systolic left ventricular pressure, left ventricular end diastolic pressure, peak positive dp/dt, peak negative dp/dt, and at the 40 mg dose there was a significant decrease in cardiac output. However, in a study of oral dronedarone compared with placebo there was no significant between group difference in 6-minute walk test, LVEF, cardiothoracic ratio or change in NYHA classification.

### **Bioavailability**

Absolute bioavailability of dronedarone is 15% under fed conditions. Food increases exposure to dronedarone by seven fold. A fat rich meal further increases the bioavailability of dronedarone. Bioequivalence was demonstrated between the Phase II and Phase III formulations of dronedarone.

### **Pharmacokinetics and metabolism**

*In vitro* studies indicate that

- Dronedarone is 98.4 to 98.9% bound to serum albumin, 77.6 to 88.6% bound to  $\alpha$ 1-acid glycoprotein, and this protein binding is non-saturable.
- The major metabolite of dronedarone, SR35021, has non-saturable binding of 94.5 to 95.3% to serum albumin, but has saturable binding to  $\alpha$ 1-acid glycoprotein, ranging from 73.4% at 25 ng/mL to 29.8% at 50,000 ng/mL.

- In vitro, diltiazem, nifedipine, ticlopidine, verapamil and quinidine inhibited the *N*-debutylation of dronedarone by more than 30% and ketoconazole almost completely blocked the *N*-debutylation of dronedarone.
- Dronedarone does not significantly inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1, CYP2D6, CYP3A4; CYP2B6; or CYP2C8
- SR35021 is unlikely to have significant inhibition of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4; CYP2B6; or CYP2C8 at the plasma concentrations observed in clinical studies.
- CYP3A accounts for approximately 20% of SR35021 metabolism.
- Dronedarone did not induce CYP1A2 or CYP3A4 in vitro.
- CYP3A is the primary CYP family involved in the *N*-debutylation of dronedarone to SR35021.
- More than 84% of the hepatic metabolic clearance of dronedarone was due to CYP3A4 activity.
- Dronedarone exhibits transepithelial transport with a “basal to apical”/“apical to basal” ratio of 2.5; and in addition inhibits the efflux of vincristine and digoxin with a similar potency to cyclosporine and a greater potency compared to verapamil and quinidine.

Hence there is significant potential for drug interactions with dronedarone, due to both inhibition of metabolism of dronedarone by CYP3A4 and inhibition of transmembrane solute transporters by dronedarone.

Studies in human subjects indicated dose proportionality for single oral dosing. Dose proportionality for single intravenous dosing was demonstrated. The in-vivo metabolism of dronedarone was investigated. Multiple dose studies were conflicting: there was some evidence of no autoinduction or inhibition of SR35021 production, but other evidence of  $t_{1/2}$ , AUC and  $C_{max}$  increasing with repeat dose studies.

Systemic exposure to dronedarone is increased in the elderly males compared with young males by around 25%, and in elderly females compared with elderly males by around 50%. In the efficacy studies, there was 16% lower clearance in female than in male patients and clearance decreased with increasing age. There is no significant effect of hepatic impairment upon dronedarone exposure, but exposure to SR35021 is decreased in hepatic impairment. Dronedarone and SR35021 pharmacokinetics are not altered by renal impairment.

Dronedarone increases digoxin maximum plasma concentrations ( $C_{max}$ ) by 17% when given at a dose of 400 mg once daily and by 75% when given at a dose of 400 mg twice daily, which is the recommended dosing regimen. Dronedarone increases plasma concentrations of propranolol by 16% to 33%. Dronedarone increases verapamil plasma concentrations by around 40%. Dronedarone increases plasma concentrations of metoprolol, simvastatin and nisoldipine. Plasma concentrations of ethinylestradiol and levonorgestrel are increased slightly by co-administration of dronedarone as are those of losartan. Dronedarone reduces theophylline plasma concentrations by 17%. Dronedarone has no clinically significant effect upon warfarin pharmacokinetics, and a slight increase in INR.

Ketoconazole markedly increases plasma concentrations of dronedarone. Grapefruit juice co-administration results in a 2.5 to 4 fold increase in dronedarone plasma concentrations. Verapamil increases dronedarone plasma concentrations by around 40%. Plasma concentrations of dronedarone were significantly increased by both diltiazem and nifedipine and increased slightly by nisoldipine. Rifampicin significantly decreases plasma concentrations of dronedarone. There is no effect on dronedarone pharmacokinetics for pantoprazole or losartan.

## **Efficacy**

The 400 mg twice daily dose was superior to placebo, dronedarone 600 mg twice daily and dronedarone 800 mg twice daily, as demonstrated by an increase in time to first AF recurrence and



an increase in time to treatment failure, the primary clinical efficacy outcome measures. For secondary efficacy outcome measures, there was an increasing proportion of patients reverting without electrical cardioversion with increasing dronedarone dose and ventricular rate in case of recurrence was lower in the dronedarone groups. Overall, there was no clinical advantage in increasing the dose beyond 400 mg twice daily.

In patients with AF, dronedarone decreased ventricular rate, and this decrease was maintained for at least 4 months. Dronedarone decreased the risk of first recurrence on AF/AFL by 12 months by 22%, and also ventricular rate was reduced in the event of first recurrence. The risk of AF/AFL recurrence was decreased by Day 30 of treatment and maintained over the 12 month follow-up period. The risk of symptomatic first recurrence was also reduced over the 12-month follow up. In *Study EFC4788 ADONIS* there was a decrease in the risk of recurrence of 11.7% at 12 months with dronedarone.

In patients with age  $\geq 70$  years, hypertension, diabetes, prior cerebrovascular accident or systemic embolism; and/or CHF there was a decrease in first cardiovascular hospitalization or death from any cause was apparent throughout a 30 month follow-up period. The risk of cardiovascular hospitalisation was reduced in the dronedarone group and the risk of cardiovascular death was decreased in the dronedarone group. However there was no difference in the risk of all-cause death.

In Study Efc4968 DIONYSOS amiodarone was demonstrated to be superior to dronedarone for the composite endpoint of: either first recurrence of AF, and/or premature study drug discontinuation for intolerance (discontinuations due to an AE and all discontinuations not due to administrative reasons) or lack of efficacy.

In Study Efc4968 DIONYSOS there were similar proportions of subjects with SAEs in the dronedarone and amiodarone treatment groups. However, overall there were fewer AEs in the dronedarone treatment group. Bradycardia, sleep disorder, dizziness, headache, tremor, hypothyroidism and peripheral oedema were reported more frequently in the amiodarone group. Abnormalities in thyroid function tests were more common in the amiodarone group. Haemorrhagic events were reported at a significantly higher rate in the amiodarone group and at Day 10, INR was greater in the amiodarone group. There were five deaths in the amiodarone group and two in the dronedarone group. Serum creatinine increased to a greater extent in the amiodarone group than the dronedarone group.

However, there was a significantly higher risk of gastrointestinal events in the dronedarone group and marked elevations in AST or ALT were more common in the dronedarone group.

There were two studies conducted for a different route than that applied for under the present application. In a study of intravenous dronedarone for the conversion of AF/AFL to sinus rhythm there was no significant difference between the treatment groups, but the study appeared to be underpowered. In a study of VT inducibility in patients with an ICD there was no significant effect for dronedarone.

*Study DRI3550 DAFNE*, *Study EFC4508 ERATO*, *Study EFC3153 EURIDIS* and *Study EFC4788 ADONIS* all excluded patients with clinically overt CHF. However, *Study EFC5555 ATHENA* included patients with CHF, but excluded those with NYHA grade IV. All of these studies were placebo controlled. *Study DRI3550 DAFNE* and *Study EFC4508 ERATO* were of 6 months duration. *Study EFC3153 EURIDIS* and *Study EFC4788 ADONIS* were of 12 months duration. *Study EFC5555 ATHENA* was for up to 30 months duration.

Therapeutic drug monitoring may be useful for optimising treatment.

## Safety

A total of 1998 patients were treated with dronedarone for up to 1 year, and 425 patients were treated for up to 2 years

Dronedarone was associated with an increased risk of TEAEs in comparison with placebo. There was an increased risk of nausea, vomiting and diarrhoea that was consistent across the clinical studies. Dronedarone was consistently associated with prolongation of the PR and QTc intervals. There are possible associations of dronedarone with: renal failure, drug toxicity, photosensitivity, skin infection, increased levels of cardioactive drug, dysgeusia, coronary artery stenosis, neuralgia, and restless legs syndrome. Diarrhoea, nausea and vomiting are important treatment limiting adverse events.

Except for *Study EFC5555 ATHENA* there appeared to be an increased risk of sudden and/or cardiovascular death. In subjects with CHF, *Study EFC4966* indicated an increased risk of cardiac death and for first hospitalization with CHF. This may have been related to an imbalance of treatment with ACE inhibitors or angiotensin II receptor antagonists. However, this was not apparent from the data submitted in the submission. The sponsor should submit a separate analysis where the drop-out rate for ACEI or angiotensin II receptor antagonists is demonstrated, and analysed as a covariate.

The data did not indicate an increased risk of pulmonary, hepatobiliary, haematological or ocular disorders. This might invite favourable comparisons with amiodarone, but it should be noted that because of the absence of comparator controlled trials such conclusions are limited.

A number of drug interactions were identified by the safety data. There was a significant interaction effect between propranolol and dronedarone on PQ and QTc. There was a statistically significant decrease in myocardial contractility with the combination of metoprolol and dronedarone. There was a statistically significant increase in PR interval when dronedarone was co-administered with diltiazem. There was a decrease in QT interval with dronedarone and nifedipine co-administration. PR and QTC were increased in co-administration relative to either dronedarone or verapamil as monotherapy. QTc values >450 ms were observed in five subjects during theophylline alone and ten during co-administration. Increase from baseline in QTc was more pronounced with the combination of digoxin and dronedarone.

## Deficiencies in the Submission

In the initial submission, there were no efficacy data for dronedarone in comparison with the usual medical treatment for AF/AFL in Australia. Such data, however, was provided in the supplementary submission (see discussion below).

There are insufficient data demonstrating either safety or efficacy for dronedarone as monotherapy. The proposed indications imply that dronedarone can be used as monotherapy for AF. The ATHENA trial examined dronedarone as add-on therapy in subjects that were predominantly co-medicated with beta-blockers, digitalis and/or calcium antagonists with rate lowering effects. Hence, it appears that the current level of evidence supports dronedarone only as second-line therapy, in combination with beta-blockers, digitalis and/or calcium antagonists.

One study indicates mortality benefit, but three studies (including ANDROMEDA) indicate greater mortality. In comparison with amiodarone, there appears to be lesser mortality. Overall, there is lack of clarity regarding the effect of dronedarone upon mortality. The sponsor should undertake further randomised, placebo controlled studies to demonstrate either a neutral or beneficial effect upon mortality rates.

It is not clear whether it should be recommended that dronedarone be prescribed in combination with an ACEI or angiotensin II receptor antagonist. The post-hoc analysis of death rates in the

ANDROMEDA study stratified by ACEI and angiotensin II receptor antagonist co-medication indicates increased morbidity in subjects treated with dronedarone that were not co-medicated with an ACEI or angiotensin II receptor antagonist. This possible interactive effect should be explored in further studies.

### Recommendations and Further Evaluator Comments

In the opinion of the evaluator, the application for registration of dronedarone as hydrochloride (Multaq / Dronedarone Sanofi / Dronedarone Winthrop) 400 mg tablets should be rejected because the risk benefit profile of dronedarone cannot be determined for the following reasons:

1. The absence of pivotal data comparing dronedarone with standard therapy for AF/AFL in Australia. In the absence of this data it is not possible to determine whether dronedarone should be a first line treatment, or should be reserved for patients who do not respond to standard therapy. This data should include both efficacy data and safety data, enabling a comparison of the risk benefit profile of dronedarone with that of standard therapy.
2. There are significant concerns regarding the possibility of a higher death rate with dronedarone compared with placebo. These concerns necessitate the comparison of dronedarone with standard therapy for AF/AFL in order to confirm that dronedarone does not have a significantly higher mortality than standard therapy. In the absence of data comparing dronedarone with amiodarone it is not possible to determine the risk benefit profile of dronedarone. It is apparent that there is a possible increase in mortality in patients treated with dronedarone, but it is not apparent what the difference in mortality might be in comparison with amiodarone. In addition, dronedarone does not appear to have some of the major adverse reactions of amiodarone. Prescribers might be tempted to prescribe dronedarone in preference to amiodarone (because of the apparent absence of these major adverse reactions) without due consideration of the potential difference in mortality rates.
3. The large number of drug-drug and food-drug interactions affecting dronedarone pharmacokinetics indicate that dronedarone will present considerable challenges in clinical practice. This is another reason for demonstrating either superiority or non-inferiority for dronedarone in comparison with amiodarone.
4. The post-hoc analysis of the ANDROMEDA trial with regard to the confounding effect of ACEI or angiotensin II receptor antagonist treatment is not presented in sufficient detail to enable evaluation. A further analysis should be submitted, including a tabulation of patients discontinuing ACEI and/or angiotensin II receptor antagonists and an analysis of death rates corrected for discontinuation. The drop out rates should be tabulated by ACEI and angiotensin II receptor co-medication, discontinuation from ACEI and angiotensin II receptor co-medication, and absence of ACEI and angiotensin II receptor co-medication at any stage during the study. This analysis should be presented as a separate study report in order to enable a complete evaluation.
5. The clinical data do not contain a summary or an analysis of patient exposure to study medication. A complete analysis of this data should be submitted as a separate report.

There were also a number of discussion points on the product information to which the sponsor responded in the supplementary submission. These will not be discussed in this AusPAR.

With respect to *Efficacy*, the sponsor's response to the clinical evaluation report provided the following clarifications:

- *The decreased mortality in comparison with placebo described in the ATHENA study was when dronedarone was used in addition to beta-blockers, digitalis and/or calcium antagonists with rate lowering effects. This would indicate that dronedarone should be used as a second line*

*agent, in patients who had not responded to standard therapy and in addition to beta-blockers, digitalis and/or calcium antagonists with rate lowering effects.*

- *The pooled analysis of death rates from placebo controlled studies (which excluding the results of the ANDROMEDA study) indicated a decreased risk of death in the dronedarone group that was not statistically significant: hazard ratio (95% CI), dronedarone versus placebo, 0.849 (0.668 to 1.077). The results of the pooled analysis were heavily dependent upon the results of the ATHENA study, which was the only study that independently indicated a mortality benefit for dronedarone.*
- *It remains unclear whether the determinant of increased mortality risk in the ANDROMEDA study was NYHA Class III or IV CHF, or unstable CHF. Hence the appropriate wording for the contraindication should be: Patients with NYHA Class III or IV heart failure and patients with NYHA Class II heart failure with recent decompensation requiring hospitalisation*
- *The post-hoc analysis of death rates in the ANDROMEDA study stratified by ACEI and angiotensin II receptor antagonist co-medication indicates that there was a protective effect. Death rates were slightly increased in placebo subjects who were not co-medicated, but were greatly increased in dronedarone subjects who were not co-medicated. It is not clear whether it should be recommended that dronedarone be prescribed in combination with an ACEI or angiotensin II receptor antagonist.*

The evaluator noted that the sponsor concluded a “consistent trend on total mortality in favour of dronedarone” but this is not consistent with either the data presented in the submission or the supplemental data. The only study indicating such a benefit was the ATHENA study. The EURIDIS and ADONIS studies (in addition to the ANDROMEDA study) had a greater number of deaths in the dronedarone groups. In addition, the mortality benefit was not statistically significant.

With respect to *Recommendations and Further Evaluator Comments*, the sponsor responded to each of the numbered comments by the evaluator.

*In response to comment 1, the sponsor provided data from the General Practice Research Network that indicated that in a sample of 14,500 general practitioners in Australia 40% of AF patients were treated with beta-blockers, 28% with sotalol, 22% with amiodarone and 9% with flecainide. Hence, the available comparator controlled data (from the DIONYSOS study) compared dronedarone to one of the treatments prescribed by general practitioners in Australia for AF (amiodarone).*

The evaluator noted that although amiodarone is not the most commonly prescribed treatment for AF in Australia it is still an appropriate comparator for dronedarone. The DIONYSOS study demonstrated that amiodarone was superior to dronedarone for the primary efficacy outcome measure. In the DIONYSOS study there were similar rates of SAEs for dronedarone and amiodarone, but slightly more deaths in the amiodarone group. There was a higher rate of AEs in the amiodarone group, particularly thyroid disorders and sleep disorder. There was a higher rate of gastrointestinal disorders in the dronedarone group. However, given the superior efficacy of amiodarone, and similar rate of SAEs, the risk benefit profile does not appear to be in favour of dronedarone over amiodarone.

*The sponsor also highlighted the decreased mortality in comparison with placebo in the ATHENA study.*

The evaluator noted that the ATHENA study was an add-on study where 77.6% of subjects in the dronedarone group received concomitant beta-blocker treatment 20.3% received digitalis and 19.9% received calcium antagonists with rate lowering effects. Hence, it appears that the decreased mortality in comparison with placebo was when dronedarone was used in addition to beta-blockers, digitalis and/or calcium antagonists with rate lowering effects. This would indicate that dronedarone should be used as a second line agent, in patients who had not responded to standard

therapy and in addition to beta-blockers, digitalis and/or calcium antagonists with rate lowering effects.

The evaluator also noted that the sponsor also quoted from the AFFIRM study which was not randomised and did not appear to include treatment with dronedarone. Hence the AFFIRM study does not contribute comparative efficacy data for dronedarone.

The clinical evaluator re-phrased this objection as follows:

1. The absence of data demonstrating either non-inferiority or superiority for dronedarone compared with standard therapy for AF/AFL in Australia. Further studies are required to demonstrate efficacy (either superiority or non-inferiority) in comparison with amiodarone and/or beta-blockers.

*In response to comment 2, the sponsor provided a pooled analysis of death rates from placebo controlled studies, excluding the ANDROMEDA study (Table 20). The pooled analysis indicates a decreased risk of death in the dronedarone group that was not statistically significant: HR (95% CI), dronedarone versus placebo, 0.849 (0.668 to 1.077).*

Table 20: Summary of analysis of time from randomisation to death from any cause during the on-study period, all randomised and treated subjects

Studies	Number of patients with endpoint		Relative Risk [95% CI] <sup>a</sup>
	Placebo	Dronedarone 400mg BID	
DRI3550/DAFNE	0 (N=66)	0 (N=76)	No deaths reported
EFC3153/EURIDIS	0 (N=201)	2 (N=411)	No deaths reported
EFC4788/ADONIS	5 (N=208)	9 (N=417)	0.794[0.266-2.370]
EFC4508/ERATO	1 (N=89)	1 (N=85)	1.066[0.067-17.046]
EFC5555/ATHENA	139 (N=2311)	116 (N=2293)	0.841[0.657-1.076]
AF/AFL Population <sup>b</sup>	145 (N=2875)	128 (N=3282)	0.849[0.668-1.077]

<sup>a</sup> Determined from Cox regression model

<sup>b</sup> Relative risk from Cox model is adjusted on studies

*The sponsor argued that the results of the ANDROMEDA study should not be included in this analysis because the subjects in that trial had unstable CHF.*

However, the evaluator noted that the exclusion criteria (regarding CHF) for the ATHENA study is stated as:

- Patients in unstable hemodynamic condition such as acute pulmonary edema within 12 hours prior to start of study medication; cardiogenic shock; treatment with intravenous pressor agents; patients on respirator; congestive heart failure of stage New York Heart Association (NYHA) IV within the last 4 weeks; uncorrected, haemodynamically significant primary obstructive valvular disease; haemodynamically significant obstructive cardiomyopathy; a cardiac operation or revascularization procedure within 4 weeks preceding randomization

These exclusion criteria did not exclude NYHA Class III CHF. However, in the ATHENA study only 4% of subjects had NYHA Class III CHF at baseline, whereas in the ANDROMEDA study 58.1% had Class III and 3.0% had Class IV.

*The sponsor provided further analysis of deaths in the ANDROMEDA and ATHENA trials by performing post-hoc analyses of death rate in those subjects with NYHA Class II CHF and LVEF*

<35% (Tables 21 and 22). These analyses indicate that the increased mortality seen in the ANDROMEDA study was not seen in those subjects in the ATHENA study with NYHA Class II CHF and LVEF <35%. This suggests that left ventricular function is not the determinant of increased mortality, but that it might be a confounder. The sponsor concluded that clinical instability is the determinant of the increased mortality seen with dronedarone in the ANDROMEDA study.

Table 21: Overview of death in Class II or IV patients in ANDROMEDA and ATHENA

	<b>ANDROMEDA</b>	<b>ATHENA</b>	<b>ATHENA</b>
	<b>Class III-IV</b>	<b>Class III</b>	<b>All Others</b>
	Clinically unstable	Clinically stable	Clinically stable
Total number of patients	375	200	4428
Number of patients on placebo	196	109	2218
Number of patients on dronedarone	179	91	2210
Total number of events	25	33	222
Number of events on placebo	7	21	118
Number of events on dronedarone	18	12	104
Relative risk of death (95% CI)	2.77 [1.16-6.63]	0.66 [0.32-1.34]	0.89 [0.68 – 1.16]

Table 22 Overview of death in patients with LVEF in ANDROMEDA and ATHENA

	<b>ANDROMEDA<sup>a</sup></b>	<b>ATHENA</b>	<b>ATHENA</b>
		<b>LVEF &lt; 35%</b>	<b>LVEF ≥ 35%</b>
	Clinically unstable	Clinically stable	Clinically stable
Total number of patients	627	179	4365
Number of patients on placebo	317	87	2194
Number of patients on dronedarone	310	92	2171
Total number of events	37	26	227
Number of events on placebo	12	16	121
Number of events on dronedarone	25	10	106
Relative risk of death (95% CI)	2.13 [1.07-4.25]	0.55 [0.25-1.21]	0.89 [0.69 – 1.15]

<sup>a</sup> All patients in the ANDROMEDA trial were to have had a LVEF<35%

The Sponsor proposed to deal with the increased death rate in subjects with unstable CHF by including the following statement in contraindications:

*“Patients with NYHA class IV heart failure or NYHA Class III heart failure with recent decompensation requiring hospitalisation”*

However, the evaluator noted that this does not completely explain the difference in mortality between the two studies. The inclusion criteria for ANDROMEDA include NYHA Class II CHF, and exclude the more seriously ill subjects with CHF. Hence, the number of subjects in ATHENA with NYHA Class III CHF may be too few to be able to conclude safety in this subgroup. In addition, subjects with unstable NYHA Class II CHF were included in ANDROMEDA. In the opinion of the evaluator, a more appropriate statement in the contraindications section would be:

*“Patients with NYHA class III or IV heart failure and patients with NYHA Class II heart failure with recent decompensation requiring hospitalisation”*

The clinical evaluator re-phrased this objection as follows:

2. There remain significant concerns regarding the possibility of a higher death rate with dronedarone compared with placebo. One study (ATHENA) indicates mortality benefit, but three studies (including ANDROMEDA) indicate greater mortality. In comparison with amiodarone, there appears to be lesser mortality. Overall, there is lack of clarity regarding the effect of dronedarone upon mortality. Further safety data are required in order to support the findings of the ATHENA study.

*In response to comment 3, the sponsor responded by indicating the similarities in drug interaction profile between amiodarone and dronedarone. In addition, the sponsor drew attention to the greater rate of clinically apparent interactions with anticoagulation for amiodarone compared with dronedarone in the DIONYSOS study.*

However, the evaluator noted that given the superior efficacy of amiodarone in the DIONYSOS study, the lesser impact upon anticoagulants is unlikely to tip the risk benefit comparison in the favour of dronedarone.

The clinical evaluator re-phrased this objection as follows:

3. The large number of drug-drug and food-drug interactions affecting dronedarone pharmacokinetics indicate that dronedarone will present considerable challenges in clinical practice. Although the drug interaction profile is similar to amiodarone, amiodarone has been demonstrated to be superior to dronedarone, with both appearing to be equally difficult to manage in clinical practice. A drug that has a similar interaction profile, with lesser efficacy does not appear to confer any advantage.

*In response to comment 4, the sponsor provided a post-hoc analysis of death rates in the ANDROMEDA study stratified by ACEI and angiotensin II receptor antagonist co-medication (Table 23).*

The evaluator noted that this analysis indicates that, rather than being a confounding effect of ACEI and angiotensin II receptor antagonist co-medication, there was a protective effect (that is, an interaction effect). Death rates were slightly increased in placebo subjects who were not co-medicated, but were greatly increased in dronedarone subjects who were not co-medicated. This effect was also seen to some extent in the analysis of subjects that discontinued prematurely (Table 24).

Table 23: Number of subjects who discontinued prematurely the study drug according to the intake of ACEI / angiotensin II receptor antagonists up to the 16<sup>th</sup> of January 2003, all randomised and treated subjects

	Placebo (N=317)	Dronedarone 400 mg BID (N=310)
Never interrupted concomitant ACE inhibitors or All receptor antagonists	281	249
Number (%) of patients with premature study drug discontinuation	37 (13.2 %)	49 (19.7 %)
Interrupted concomitant ACE inhibitors or All receptor antagonists	18	41
Number (%) of patients with premature study drug discontinuation after the interruption of ACE or All receptor antagonists	2 (11.1 %)	12 (29.3 %)
Never took ACE inhibitors or All receptor antagonists	18	20
Number (%) of patients with premature study drug discontinuation	7 (38.9 %)	11 (55.0 %)

Table 24: Summary of study drug exposure according to a specific time point, all randomised and treated patients in AF/AFL placebo controlled studies

	Placebo	Dronedarone 400 mg BID	Dronedarone 600 mg BID	Dronedarone 800 mg BID
Up to 3 months				
N	2414	2718	20	17
Patient-time	13364	14560	38	31
Up to 6 months				
N	2205	2517	12	9
Patient-time	6522	7132	12	9
Up to 12 months				
N	1812	1998	N/A	N/A
Patient-time	2965	3151		
Up to 18 months				
N	1156	1145	N/A	N/A
Patient-time	1456	1445		
Up to 24 months				
N	430	425	N/A	N/A
Patient-time	455	451		

N corresponds to the cumulative number of patients exposed up to the associated time point

Note: protocols : DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA

The clinical evaluator re-phrased this objection as follows:

4. It is not clear whether it should be recommended that dronedarone be prescribed in combination with an ACEI or angiotensin II receptor antagonist.

*In response to comment 5, the sponsor provided a tabular summary of patient exposure to study medication. The ANDROMEDA study has been omitted from this tabulation.*

## V. Pharmacovigilance Findings

There was no Risk Management Plan (RMP) submitted with the application as it was not a requirement at the time of submission. However, in response to questions raised by the Delegate (Section VI), the sponsor submitted an RMP and a Periodic Safety Update Report (PSUR). The RMP was found to be acceptable and well presented with most matters resolved. The pharmacovigilance plan includes routine activities, special report forms to collect information on interstitial lung disease (ILD), hepatic injury and pregnancy, disease registries, prescription surveys,



pharmacoepidemiological studies and targeted communication plans. The proposed Australian PI was compared with those from the US and EU and found to incorporate the elements of the RMP. The TGA's Office of Medicines Safety Monitoring (OMSM) has recommended a Use in Elderly section in the PI. The OMSM also noted that the pharmacoepidemiological study reports will be available in 5 years time, the sponsor has agreed to provide the prescription survey protocol and the sponsor will include a pre-treatment measurement for creatinine concentrations in the PI.

The following safety concerns were identified by the sponsor:

Important identified risks:

- Inappropriate management of the signal of serum creatinine increase
- Drug-drug interactions with potent CYP3A4 inhibitors.

Important potential risks:

- Patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with recent decompensation requiring hospitalization
- Drug-drug interactions with digoxin, calcium antagonists with heart rate lowering properties, beta-blockers, statins, tacrolimus and sirolimus, and potent CYP3A4 inducers;
- Amiodarone-like effects, not observed to date with dronedarone in the clinical program interstitial lung disease, severe skin disorders, neuropathy, including optic neuropathy, and, hepatic injury
- Preclinical finding: prolactin-induced mammary carcinogenesis.

Important missing information:

- Effect in pregnancy
- Effect in lactation
- Effect in severe hepatic impairment
- Effect in children (potential off-label use)

The sponsor proposed, in addition to routine pharmacovigilance activities, specific report forms, disease registries, prescription surveys and post marketing studies to further characterise these risks. To address the following safety concerns, additional activities that entail a targeted communication plan, drug interaction studies and pharmacoepidemiological studies were proposed:

- Inappropriate management of the signal of serum creatinine increase;
- Drug-drug interactions with potent CYP3A4 inhibitors; and
- Inappropriate use in patients with New York Heart Association (NYHA) Class IV heart failure or NYHA Class II-III heart failure with recent decompensation requiring hospitalisation.

## **VI. Overall Conclusion and Risk/Benefit Assessment**

The submission was summarised in the Delegate's overview and recommendation.

### **Quality**

Approval was recommended from a chemistry, quality control and bioavailability aspect. The evaluator noted that dronedarone is a sulphonamide drug proposed for registration in bottle sizes up to 500 tablets. However the sponsor has not submitted in use stability data to support such a large bottle size. Food affected the pharmacokinetics and it was recommended that the drug be taken

with meals. Seven bioavailability studies were submitted which showed bioequivalence between the 400mg tablet used in the phase III studies and a 200mg tablet used in the phase II studies and that low and high fat meals significantly increase dronedarone bioavailability. Neither the absolute bioavailability nor the relative bioavailability compared to an oral solution has been determined. A study using a capsule formulation indicated that absolute bioavailability in the fed state was 15% and that food increased bioavailability by 7.5 fold but these figures may not be indicative of the true values. The likely effect of food based on the formulations assessed was an increase in the AUC of 2-3 fold. The submission was considered by Pharmaceutical Subcommittee (PSC) of ADEC and no objections were raised.

## **Nonclinical**

The nonclinical evaluator has raised no objections to registration. Animal studies demonstrated reduced heart rate and left ventricular contractility, and increased atrial and AV node refractory periods, Wenckebach cycle lengths, PQ and QT intervals. Pro-arrhythmic activity was seen in dogs and slight increases in creatinine but no nephrotoxicity. Safety pharmacology studies did not reveal any untoward findings and pharmacokinetic studies showed low bioavailability, with some melanin binding and accumulation in mesenteric lymph nodes. Human hepatic metabolism was via CYP3A4 and dronedarone and/or metabolites inhibited CYP2D6 and CYP3A4. Oral administration showed phospholipidosis in lungs and mesenteric lymph nodes, slightly reduced T3 (rats and dogs) and increased testicular atrophy which may be age or hormonally related. Genotoxicity was not seen but carcinogenicity studies in mice, but not rats, showed increased adenocarcinomas at 3x expected human AUC which was associated with increased prolactin. Increased prolactin was not seen in rats but has been seen with other drugs for example, haloperidol, which also increased mouse mammary tumours. There were also some other tumours that were considered of limited relevance to humans and some cell changes were seen in mesenteric lymph nodes. Teratogenicity was seen in rats at a NOEL of 0.5x human exposure but not in rabbits, although the latter was indeterminate. Dronedarone should therefore not be used by pregnant women (Pregnancy category D proposed). A rat fertility study showed prolonged or irregular oestrous cycles at an exposure below clinical value suggesting hormonal effects and substantial milk excretion implying breastfeeding should not be undertaken. Phototoxicity was seen.

## **Clinical**

**DAFNE:** The primary efficacy endpoint of time to first recurrence of AF after conversion to sinus rhythm using ECG, TTEM (trans-telephonic ECG monitoring) or telemetry showed a significant effect for 400mg twice daily (bd), but not for the other groups (median 56 days versus 5 days placebo). Reversion to sinus rhythm without electrical cardioversion increased with dronedarone dose. Ventricular rate in case of recurrence was lower with dronedarone. There was no difference in the number of DC shocks or joules required. The PR interval increased with dose. No lower dose of dronedarone was investigated.

**ERATO:** The primary efficacy endpoint of change in mean heart rate measured by 24hr Holter monitoring on Day 14 showed a greater decrease in ventricular rate on dronedarone than placebo (-11.7bpm [95%CI: -14.8, -8.5]). There was no difference in duration of maximal exercise, but a reduction in heart rate at sub-maximal (-23 bpm) and maximal exercise (-24 bpm) on dronedarone. A reduction in systolic BP was seen of 7-9 mmHg at rest and sub-maximal exercise but not for maximal exercise. A maintenance of reduction in heart rate was seen at 4 months (-8.8 bpm) and a trend for conversion to sinus rhythm was seen with 9.4% of dronedarone versus 2.2% of placebo converting.

**EURIDIS and ADONIS:** The primary efficacy endpoint of time in days elapsed between randomisation and first documented AF/AFL recurrence (episode of >10minutes by two consecutive ECGs/TTEMs both showing AF/AFL) within 12 months showed dronedarone

significantly decreased the risk of recurrence by 22% (RR 0.784 [95%CI: 0.64, 0.96]) in the EURIDIS trial and by 27% (RR 0.725 [95%CI: 0.59, 0.89]) in the ADONIS trial. This risk decreased at Day 30 and was maintained to 12 months. Symptomatic first recurrence was also reduced at 12 months and ventricular rate at first recurrence was lower on dronedarone (mean 100 versus 112 bpm in EURIDIS and 103 versus 111 bpm in ADONIS). The effect of dronedarone on time to first recurrence of AF/AFL was significant in the high and low trough plasma concentration group suggesting therapeutic drug monitoring of trough concentrations might be useful.

**ATHENA:** The primary efficacy endpoint which was a composite of time from randomisation to first occurrence of cardiovascular hospitalisation or death from any cause showed dronedarone significantly reduced cardiovascular hospitalisation or death by 24.2% (RR 0.758 [95%CI: 0.688, 0.835]) and an absolute risk reduction of 7.4% (NNT 14). The effect was apparent through to 30 months but there was considerable loss of patients with time. The difference was not influenced by baseline demographics or disease characteristics. The primary endpoint benefit for dronedarone was driven entirely by cardiovascular hospitalisation and not by a reduction in death from any cause. All cause mortality was not significantly different from placebo. Cardiovascular mortality was significantly reduced by 30% but given that overall mortality was not significantly reduced then this result for cardiovascular mortality is exploratory only. Cardiovascular hospitalisation was significantly reduced by 25% but this is the major component of the primary endpoint.

ATHENA: Unadjusted analysis of time from randomization to first cardiovascular hospitalization or death from any cause – all randomized patients

	Placebo (N= 2327)	Dronedarone 400mg BID (N= 2301)
Number of events, n	917	734
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at 6 months [95% CI]	0.202 [ 0.185 ; 0.218]	0.147 [ 0.132 ; 0.161 ]
Cumulative incidence of events at 1 year [95% CI]	0.302 [ 0.283 ; 0.320]	0.228 [ 0.211 ; 0.245 ]
Cumulative incidence of events at 2 years [95% CI]	0.422 [ 0.400 ; 0.444]	0.354 [ 0.332 ; 0.377 ]
Endpoint's composition:		
Cardiovascular hospitalization	859	675
Death from any cause	58	59
- Cardiovascular death	33	26
- Non cardiovascular death	25	33
Log-rank test p-value	2E-8	
Relative risk [95% CI] <sup>a</sup>	0.758 [ 0.688; 0.835]	

<sup>a</sup> Determined from cause-specific Cox regression model

Note: deaths, cardiovascular or non-cardiovascular, were only those not preceded by hospitalization.

**DIONYSOS:** The primary efficacy endpoint of either first recurrence of AF and/or premature study drug discontinuation for intolerance or lack of efficacy showed a 59% increase for dronedarone compared to amiodarone with HR 1.59 (95%CI 1.28, 1.98), indicating amiodarone was superior to dronedarone. Treatment failures were higher on dronedarone (74 versus 55%) and these failures also occurred sooner on dronedarone (41 versus 183 days). The components of the primary endpoint indicated that the superiority of amiodarone was driven by a higher rate of recurrence of AF on dronedarone (64 versus 42%).

The sponsor also submitted studies using IV dronedarone in treating atrial fibrillation and suppressing ventricular tachycardia.

Total exposure to dronedarone was 4867 subjects with 1998 treated for up to one year and 425 for up to two years. Treatment-limiting adverse events consisted of diarrhoea, nausea and vomiting. There did not appear to be an increased risk pulmonary, hepatobiliary, haematologic or ocular disorders. A pooled analysis from the healthy volunteer studies showed headache, dizziness and bradycardia were the most common adverse events. A pooled analysis of studies in AF/AFL

showed possible associations with dronedarone include renal failure, drug toxicity, photosensitivity, skin infection, dysgeusia, coronary artery stenosis, neuralgia and restless leg syndrome. Serious adverse events showed a similar pattern to placebo although slightly higher heart failure (0.5 versus 0.2%).

The dose ranging study, **DAFNE**, showed serious adverse events and arrhythmia were higher in the higher dose groups. Dronedarone was associated with decreases in haemoglobin, increases in transaminases and increases in creatinine and an inverse relationship between heart rate and trough plasma concentrations and QTc. The **ERATO** study showed treatment emergent adverse events (TEAE) were less on dronedarone than placebo with the most common being nasopharyngitis, influenza, dyspnoea and diarrhoea. Serious adverse events and discontinuations due to adverse events were slightly higher on dronedarone than placebo, along with serum creatinine increased (+10.6 µmol/L), digoxin levels (+41%), transaminases, QTc and bradycardia. The **EURIDIS** study showed TEAE were similar to placebo, serious adverse events were higher on placebo and discontinuations due to adverse events were slightly higher on dronedarone, along with increased serum creatinine (+8.8 µmol/L) and prolongation of PR and QTc interval, including those with ≥500ms (6.4 versus 0.5%) and increase from baseline of 30-60 ms (40 versus 29%) and >60 ms (16.8 versus 7%). Changes in liver enzymes and thyroid function were similar to placebo. The **ADONIS** study showed slightly higher TEAE on dronedarone, including diarrhoea, nausea, vomiting, arthralgia, back pain, respiratory infection and myalgia. Serious adverse events were similar to placebo except cardiac failure which was higher on dronedarone (1.4 versus 0.5%). Discontinuations due to TEAE were slightly higher on dronedarone, along with serum creatinine (+11.9 µmol/L) and PR and QTc prolongation, including those with ≥500 ms (5.4 versus 3.8%) and increase from baseline of 30-60 ms (41 versus 25%) and >60 ms (12 versus 4%). Thyroid function and liver enzyme changes were similar to placebo. The **ATHENA** study showed TEAEs were similar between dronedarone and placebo but increases were seen on dronedarone for diarrhoea, nausea, fatigue, bradycardia (3.5 versus 1.2%) and creatinine (4.7 versus 1.3%). Serious adverse events were higher on placebo, but acute renal failure was higher on dronedarone (0.6 versus 0.2%). Discontinuations due to TEAEs were higher on dronedarone, mainly diarrhoea, nausea, fatigue, and QTc prolongation. Changes were seen in serum creatinine (+10 µmol/L), digoxin (+0.4 nmol/L), diastolic BP (-3 mmHg), bradycardia (10.6 versus 4.2%), PR interval prolongation (40 versus 26%) and QTc (≥500 ms was 6.6 versus 4.2%), increase from baseline of 30-60 ms (35 versus 26%) and >60 ms (16 versus 10%). The **DIONYSOS** study had a primary safety endpoint of occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye or gastrointestinal events or premature drug discontinuation following an AE which occurred in 33% dronedarone versus 42% amiodarone (HR 0.80, 95%CI 0.60, 1.07). Most of these events were higher on amiodarone (for example, thyroid disorders 5.9 versus 0.8%) except for hepatic events (12 versus 11%) and gastrointestinal events (13 versus 5%, HR 1.98) which were higher on dronedarone. Overall adverse events showed bradycardia, bradyarrhythmias (10.6 versus 3.6%), haemorrhagic events (11.4 versus 5.6%), sleep disorder, hypertension, dizziness, headache, tremor, hypothyroidism and peripheral oedema were more common on amiodarone. Serious adverse events and discontinuations due to adverse events were slightly higher on amiodarone, as too were increases in serum creatinine (8.1 versus 4 µmol/L) and abnormalities in thyroid function tests. Deaths from all trials are discussed below.

The pharmacology studies showed similar adverse events to the clinical trials, however the interaction studies showed more TEAEs with pantoprazole, increased PR interval with ketoconazole (+13 ms), decreased PR interval with rifampicin, reduced myocardial contractility with metoprolol, increased PR interval with diltiazem (+14 ms), decreased QT interval with nifedipine, increased TEAEs with nisoldipine, notably headache and palpitations, prolonged PR and QTc with verapamil, increased TEAEs with losartan, increased PQ and QTc with propranolol, increased QTc with theophylline and increased QTc with digoxin. The hepatic impairment study showed prolonged QTc in 7 of 9 patients compared with none in healthy volunteers. A study in patients with an

implantable cardioverter defibrillator showed increased TEAEs and serious adverse events, along with transaminase elevations (9.6 versus 0%).

**ANDROMEDA:** This was a randomised, double blind, placebo controlled study of 400 mg twice daily dronedarone for 12 months in 627 patients with congestive heart failure (39% NYHA Class II, 58% NYHA Class III, 3% NYHA Class IV, no Class I). The study was terminated after 7 months (mean exposure 63 days) due to increased mortality in the dronedarone arm and the DSMB recommended follow up for mortality, major clinical events and renal function. At baseline patients were similar for AF/AFL, but paroxysmal and first episode AF differed. Patients also differed with more ischaemic heart disease, coronary artery bypass grafting, hypertension, alcohol induced cardiomyopathy and diabetes in the dronedarone arm. The primary efficacy endpoint of death from any cause or hospitalisation for worsening heart failure was higher on dronedarone (RR 1.38, 95% CI 0.92, 2.09) and increased slightly with duration of treatment. The absence of ACE inhibitors or angiotensin II receptor blockers (ARBs) might be associated with increased risk. Mortality was higher on dronedarone (25 versus 12 deaths, RR 2.13, 95%CI 1.07, 4.27) with the majority being cardiovascular deaths (96% for dronedarone, 75% for placebo). Again mortality was associated with absence of ACE inhibitors or ARBs but also creatinine clearance <50 mL/min, CHF >NYHA Class II and digoxin. The other component of the primary endpoint, hospitalisation for worsening heart failure, showed no difference to placebo. First hospitalisation for any heart failure was greater on dronedarone. Cardiac failure (14.8 versus 8.5%), cough, diarrhoea and hypotension were more common on dronedarone. The commonest cause for discontinuation was cardiac failure. Bradycardia and prolonged PR and QTc interval were also seen.

The reasons why the evaluator recommended rejection in the primary report included:

- No clinical data in comparison with standard treatments for AF/AFL, for example, amiodarone or digoxin.
- Possibility of a higher death rate on dronedarone compared to placebo.
- Large number of drug-drug and drug-food interactions.
- Lack of detail concerning the Andromeda study for the effect of ACE inhibitors or angiotensin II receptor blockers (ARBs) on discontinuation and death rates.
- Lack of information on patient exposure to dronedarone.

The reasons why the evaluator recommended rejection in the supplementary report included:

- Lack of data demonstrating non-inferiority or superiority of dronedarone compared to standard therapy, including amiodarone or beta-blockers.
- Insufficient data demonstrating safety and efficacy for dronedarone as monotherapy and therefore data only support second line therapy.
- Lack of clarity on whether dronedarone should be prescribed with an ACE inhibitor or ARB.
- Possible higher death rate compared to placebo but lower death rate compared to amiodarone.
- Large number of drug-drug and drug-food interactions.

## **Initial Risk-Benefit Analysis**

### **Efficacy**

The data demonstrated that 400mg twice daily (bd) was the preferred dose, but the dose ranging study did not investigate a lower dose of dronedarone for its efficacy or safety and thus the lower limit of effective dosing is unknown. The 400mg bd dose was demonstrated to be superior to placebo in patients with persistent AF for time to first recurrence of AF after conversion to sinus

rhythm, demonstrated to be superior to placebo in patients with symptomatic permanent AF for a greater decrease in ventricular rate at 4 months, demonstrated to be superior to placebo for decreasing the risk of AF/AFL recurrence at 12 months (22% in one trial and 27% in another) and superior to placebo in patients in sinus rhythm and in AF/AFL and at least one risk factor for reducing cardiovascular hospitalisation over 12-30 months. Although the primary endpoint was a composite that included all cause mortality, dronedarone had no effect on it, leaving the primary endpoint to be entirely attributable to a reduction in cardiovascular hospitalisation. Cardiovascular mortality as a subset of overall mortality was noted to be reduced on dronedarone. The comparator trial with amiodarone used a dose that was different to the Australian PI but was not expected to impact significantly on efficacy. It showed that amiodarone was superior to dronedarone in first recurrence of AF and/or premature study drug discontinuation for intolerance or lack of efficacy. More patients also failed treatment on dronedarone than they did on amiodarone and sooner.

## **Safety**

The trials noted increased TEAEs for dronedarone compared with placebo for diarrhoea, nausea and vomiting. There did not appear to be an increased risk of pulmonary, hepatobiliary, haematologic or ocular disorders. Thyroid function and liver transaminases were increased in some trials and similar to placebo in others. There appears to be some safety advantage to using dronedarone over amiodarone. Possible associations with dronedarone included renal failure, drug toxicity, photosensitivity, skin infection, dysgeusia, coronary artery stenosis, neuralgia and restless leg syndrome. Serious adverse events showed a similar pattern to placebo although slightly higher heart failure. Bradycardia, cardiac failure and prolongation of PR and QTc intervals were seen across the trials along with increases in serum creatinine. The interaction studies often showed increases in PR and QTc intervals. The safety data in comparison with amiodarone favoured dronedarone, although this was not significant for the primary safety endpoint. Dronedarone had less bradycardia, haemorrhagic events, thyroid disorders, rises in serum creatinine, bradyarrhythmias, sleep disorder, hypertension, dizziness, headache, tremor, hypothyroidism and peripheral oedema than amiodarone but more gastrointestinal adverse events.

## **Heart failure trial and boxed warning**

The Andromeda trial has demonstrated an increased risk of death when dronedarone is used in patients with NYHA Class II-IV congestive cardiac failure. This risk was seen early on and increased with time. The trial also showed no significant difference in reducing hospitalisation due to worsening heart failure. These are serious findings which contributed to the clinical evaluator's recommendation for rejection. The pivotal trials submitted for AF/AFL also excluded patients with congestive heart failure with NYHA functional Class III-IV patients (ATHENA Class IV only, but too few with NYHA Class III were included for safety assessment). However, these data are from a different population to the one being requested in this submission and therefore should not necessarily preclude registration for AF/AFL based on increased mortality in another population. It may be possible to manage this risk through appropriate warnings in the PI. The sponsor has proposed a contraindication for patients with heart failure NYHA Class III-IV, however this should be extended to NYHA Class II with recent decompensation requiring hospitalisation as recommended by the clinical evaluator. Given the seriousness of the increased mortality, prescribers should be made clearly aware of this through the use of a boxed warning. The US PI includes a boxed warning and has also included NYHA Class II patients in the contraindications. The data also suggested, based on a post-hoc analysis of deaths in the Andromeda study, that ACE inhibitors and ARBs may have played a protective role. Further study is needed to clarify if dronedarone should be used with ACE inhibitors or ARBs.

## Deaths

There were a number of deaths reported across the clinical trial program and these have been summarised below for patients on the proposed dose versus placebo. The total for AF/AFL population shows fewer deaths on dronedarone with the RR 0.85 (95%CI 0.67, 1.08), including for the largest study, ATHENA, showing fewer deaths on dronedarone. The active comparator trial, DIONYSOS also showed fewer deaths on dronedarone although the trial size is too small to be conclusive. In comparison, the ANDROMEDA study in heart failure patients showed a significantly increased risk of death, RR 2.13 (95%CI 1.07, 4.25). It would appear from these data that the risk of death with dronedarone when used as indicated in the AF/AFL patients and excluding those with congestive heart failure with NYHA functional class III-IV patients, is not increased compared with placebo and trended less than placebo.

**Table 1 - Summary of analysis of time from randomisation to death from any cause during the on-study period (all randomised and treated patients)**

Studies	Number of patients with endpoint		Relative Risk [95% CI] *
	Placebo	Dronedarone 400mg BID	
DRI3550/DAFNE	0 (N=66)	0 (N=76)	No deaths reported
EFC3153/EURIDIS	0 (N=201)	2 (N=411)	Not applicable
EFC4788/ADONIS	5 (N=208)	9 (N=417)	0.794[0.266-2.370]
EFC4508/ERATO	1 (N=89)	1 (N=85)	1.066[0.067-17.046]
EFC5555/ATHENA	139 (N=2311)	116 (N=2293)	0.841[0.557-1.076]
Total AF/AFL Population <sup>b</sup>	145 (N=2875)	128 (N=3282)	0.849[0.668-1.077]

\* Determined from Cox regression model

<sup>b</sup> Relative risk from Cox model is adjusted on studies

Note: Protocols : DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA

**Table 2 Summary of patients with endpoint of death from any cause in DIONYSOS**

Study	Number of patients with endpoint	
	Amiodarone	Dronedarone 400mg BID
DIONYSOS	5 (N=255 )	2 (N=249)

**Table 3 Summary of patients with endpoint of death from any cause in ANDROMEDA (all randomised and treated patients)**

Study	Number of patients with endpoint		Hazard Ratio [95% CI]
	Placebo	Dronedarone 400mg BID	
ANDROMEDA	12 (N=317)	25 (N=310)	2.13 [1.07; 4.25]

## Standard therapies

One of the evaluator's concerns were lack of data comparing dronedarone to standard therapies used in Australia for AF/AFL, which based on General Practice Research Network data consists of 40% beta blockers, 28% sotalol, 22% amiodarone and 9% flecainide. The sponsor has addressed this concern with the DIONYSOS study but has not submitted a study using other treatments, for example beta blockers. Whilst the DIONYSOS study showed significantly superior efficacy for amiodarone, it trended to favour dronedarone for safety. It appears that amiodarone would still be

favoured for efficacy but if there was a safety concern, then dronedarone may be appropriate in light of the efficacy demonstrated in the placebo controlled studies. It is not a requirement that active comparator trials be submitted to demonstrate non-inferiority or superiority against standard therapies for registering a new medicine, but it is nevertheless highly encouraged. Given the demonstration of efficacy in the placebo controlled trials and acceptable safety profile in light of the comparison with amiodarone, then this should not be a reason for precluding registration.

## **Second Line therapy**

The evaluator commented that dronedarone should be second line therapy in patients with standard therapies, in light of the superior efficacy of amiodarone and the numerous background therapies used in the clinical trials for example, beta blockers, digitalis and calcium channel blockers. However, the ATHENA study had a pre-specified sub-group analysis which showed that the primary endpoint was efficacious in those with or without concomitant therapies, including beta-blockers, digitalis and calcium channel blockers. Given this and that the studies submitted did not test the hypothesis of failure of amiodarone or other therapies as such, then providing the description of the clinical trials is clear that patients were on conventional therapies for their AF/AFL, then the indication as first line would be appropriate.

## **Exclusion criteria**

The clinical trials excluded patients with congestive heart failure with NYHA functional Class III-IV patients (ATHENA Class IV only), patients with bradycardia (<50 bpm) and second or third degree AV block. The ATHENA trial also excluded haemodynamically unstable patients and those with permanent AF.

## **500 tablet bottle**

The sponsor proposed a 500 tablet bottle for registration however it is unclear why such a bottle size was required. No in use stability data has been provided for this presentation, therefore it is unclear if the tablets will remain stable over time with multiple openings of the bottle, for example, moisture. Although the presentation is in a child resistant container, there is no statement on the label that the product is for dispensing only and not to be given to an individual patient. The sponsor should provide in-use stability data for this presentation and appropriate label statements.

## **Types of AF (permanent, persistent, paroxysmal) and AFL**

The studies included patients with persistent, permanent and non-permanent AF, however the pivotal Athena trial excluded patients in permanent AF. It was also noted that the US and Europe did not approve permanent AF in their indications. Given ATHENA excluded patients with permanent AF, then the Australian Drug Evaluation Committee's (ADEC) advice was requested if the indication here should include this group.

## **Atrial Flutter**

The trials only included limited numbers of patients with AFL, therefore it was unclear if the indication should support atrial flutter. Both Canada and Europe have excluded AFL from the indication but the US has included it. Given it is unlikely to have a trial in purely AFL patients and the similar pharmacological treatments as AF, then its inclusion in the indication would appear reasonable.

## **Pharmacology**

There were a significant number of drug interactions demonstrated and the sponsor should ensure these are all included in the PI. These may be challenging in clinical practice but it was noted that amiodarone also has challenging drug interactions.



## Summary

The clinical trials have demonstrated that dronedarone when compared to placebo was able to prolong the time to first recurrence of AF after conversion to sinus rhythm, decrease the ventricular rate, decrease the risk of AF/AFL recurrence and reduce cardiovascular hospitalisation in selected populations, but not all cause mortality. Its efficacy compared to amiodarone was inferior for first recurrence of AF and/or premature study drug discontinuation for intolerance or lack of efficacy. For safety, gastrointestinal adverse events were most common and there did not appear to be an increased risk of pulmonary, hepatobiliary, haematologic or ocular disorders. Thyroid function and liver transaminases were increased in some trials and similar to placebo in others. There appears to be some safety advantage to using dronedarone over amiodarone but inferior efficacy. Mortality was less on dronedarone than placebo and appeared less than on amiodarone but the trial was of small size. A significant increase in mortality was seen in heart failure patients and this group should be clearly identified and contraindicated in the PI. On balance, the risk/benefit profile appears favourable to support registration.

The Delegate proposed to approve this submission by to register this new chemical entity, dronedarone, for the treatment of patients with atrial fibrillation or atrial flutter, based on the quality, safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above in the Risk / Benefit Discussion:

*Multaq is indicated in patients with paroxysmal or persistent atrial fibrillation or atrial flutter to reduce the risk of cardiovascular hospitalisation (see Clinical Trials).*

The Delegate indicated that the sponsor should address the following issues in their Pre-ADEC response:

1. A justification for a 500 tablet bottle size and what labelling will be included on the bottle, for example, for dispensing only and this pack is not to be given to an individual patient. The sponsor should also submit in use stability data to support this presentation.

*The sponsor confirmed that this pack size will only be used in hospitals and for Webster packing and not be dispensed to an individual patient. As such, a label stating 'For hospital use and Webster packing only. Bottle not to be dispensed to patient' is proposed. In reference to the stability data, the risk of contamination/degradation following repeated bottle opening is not anticipated for dronedarone, as this is clearly less significant for a film-coated tablet than for a liquid or semi-solid dosage form. Dronedarone film-coated tablets are stable and do not require any special storage condition. When stored under high level of humidity (that is, 65% or 75% RH), they showed no change regarding degradation products or physico-chemical characteristics, in particular dissolution. Moreover, the risk of microbiological contamination was evaluated at the completion (36 months) of the primary stability studies in a 500 mL bottle (500 count) and no modification was observed.*

2. Updated GMP certificates for any expired manufacturing sites.

This was done.

3. Comment on the carcinogenicity findings seen in animals and the implication for humans exposed long term to dronedarone.

*The sponsor confirmed that the findings in the carcinogenicity studies consisted of increased incidence of mammary gland epithelial tumours in the female mouse, increased incidence of histiocytic sarcomas in the mouse (with statistical significance in the male only) and, vascular changes (mainly haemangiomas) in the mesenteric lymph nodes in the male rat. These changes were observed in a single species (either mouse or rat) and one or the other sex and at the highest doses with an exposure multiple 5 to 10 times the therapeutic human exposure. In addition, these*

*findings were either considered incidental (histiocytic sarcomas), species specific with a potential mechanism of little relevance to human (mammary gland adenocarcinomas associated with hyperprolactinaemia) or to not represent a significant risk for humans (vascular changes in mesenteric lymph nodes considered as reactive-proliferative in relation to local phospholipidosis and completely innocuous). In conclusion, the weight of evidence based on arguments presented above and the non-genotoxicity of dronedarone support the conclusion that the carcinogenicity findings do not raise any significant concerns to humans exposed long-term to dronedarone.*

4. Comment on why prolactin levels were not measured in clinical trials and the implications for patients of the elevated prolactin levels seen in animals.

*The sponsor responded that as described above, the slightly increased incidence of mammary gland epithelial tumours in the female mouse at 300 mg/kg/day was associated with a slight hyperprolactinaemia that was shown by measurement of prolactin levels in two separate dedicated studies (one single dose study and one repeat-dose study performed at that dose level) and consistent with other histopathological changes noted in the mouse carcinogenicity study. The human relevance of rodent prolactin-induced mammary carcinogenesis is believed to be low. Despite extensive clinical use of many marketed compounds that are potent inducers of rodent mammary tumours by hormonal mechanisms, there is to date no evidence that these compounds induce mammary tumours in humans. Since elevated prolactin levels seen in the mouse were considered of very low relevance for humans, there was no specific plan to prospectively assess this safety topic in clinical trials, and no signal of mammary tumour has emerged from the clinical development experience. Following the same pharmacovigilance approach, prolactin-induced mammary carcinogenesis will be monitored through the signal detection process as part of the sponsor's routine pharmacovigilance system.*

5. Provide a table showing the pooled analysis from all AF/AFL clinical trials in patients for QTc Bazett's corrected for >500ms, increases of 30-60ms and >60ms increase comparing dronedarone 400mg bd versus placebo and amiodarone.

This was done.

6. Discuss why the US and Europe did not include permanent AF patients in their indication.

*The sponsor noted that this is related to the fact that both indications reflect the population of the ATHENA study in which permanent AF patients were excluded.*

7. The numbers of patients with atrial flutter across the clinical trials and any analyses on efficacy or safety that compared this group with those with atrial fibrillation or the whole AF/AFL group.

*The sponsor responded that in the clinical trials and in line with the epidemiological data, the proportion of patients with AFL was about 10%. In the ATHENA study, there were 55/531 patients with AFL in the placebo group and 49/520 in the dronedarone group at baseline, representing 10.4% and 9.4% of patients, respectively, who entered into the study with an ECG at baseline in AF or AFL. Results on the primary endpoint (cardiovascular hospitalisation or death) are consistent in patients with AFL at baseline and other cohorts of patients included in the ATHENA study. In addition, the primary endpoint (time from randomisation to first adjudicated recurrence of AF/AFL) has been analysed on patients with AFL in the EURIDIS/ADONIS pooled population. Results show that dronedarone significantly prolonged the time to first occurrence of an AF/AFL episode after randomisation compared to placebo in this population.*

8. Please advise of your Risk Management Plan for dronedarone in Australia, including collection of data relating to pulmonary toxicity, neuropathy, skin reactions and any exposure in patients with heart failure.

*The sponsor responded that the continuous assessment of all potential risks of dronedarone during its development has identified the three following important risks that require special attention for minimisation beyond labelling during the post-marketing use of the drug:*

- *Patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with recent decompensation requiring hospitalisation.*
- *Drug-drug interactions with potent CYP3A4 inhibitors*
- *Inappropriate management of the signal of serum creatinine increase*

*The sponsor has developed risk minimisation communication tools with the main goal of preventing the use of dronedarone in patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with recent decompensation requiring hospitalisation, drug-drug interactions with potent CYP3A4 inhibitors and the inappropriate management of the signal of serum creatinine increase. The communication tools have been developed in collaboration with leading Australian electrophysiologists. The communication tools include letters for specialist physicians, general practitioners and pharmacists to educate on appropriate patient selection and management regarding dronedarone to be sent at the time of launch. For the patients, a Patient Information Card has been developed to assist the prescribing physician in engaging the patients in identifying the signs and symptoms of heart failure. Educational activities, including lectures and case study presentations are planned to educate prescribers on dronedarone to minimise risk.*

*In addition to routine pharmacovigilance activities to monitor the overall safety profile of dronedarone, important potential risks have been considered for additional post-marketing monitoring. They consist of Amiodarone-like effects, not observed to date with dronedarone in the clinical program: interstitial lung disease, severe skin disorders, neuropathy including optic neuropathy and hepatic injury. The planned pharmacovigilance activities comprise the use of specific report forms to document spontaneous reports of interstitial lung disease and potential hepatic injury, and the UK database, the Health Improvement Network (THIN) and the US claims database, LabRx retrospective nested case-control studies of the safety outcomes of interest. No minimisation actions have been proposed so far, as there has been no evidence of such risks with the use of dronedarone to date.*

The Delegate also requested that the ADEC consider the following questions:

Are the data adequate to approve the submission for both atrial fibrillation and atrial flutter?

Do the data support all types of atrial fibrillation, including permanent AF?

Should the PI have a boxed warning regarding the risk for patients with heart failure, similar to the US PI?

### **Advisory Committee Recommendation**

The ADEC, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, disagreed with the Delegate's proposal.

ADEC recommended rejection of the application on the grounds of unfavourable risk/benefit ratio.

The modest efficacy demonstrated by the clinical trials was not felt to outweigh the significant risks. The Committee noted concerns related to increased risks in patients who had heart failure, the agent's proarrhythmic activities, the limited long-term data and the marked increase in hepatic transaminases found in some patients that may be a signal for significant hepatotoxic potential, and the potential risks of drug interactions, which may be difficult to manage in the clinical setting.

## Further Risk-Benefit Analysis

Following the ADEC meeting, the TGA met with the sponsor and their international colleagues to discuss the submission and the Delegate requested further information from the sponsor to address the following matters of concern with their submission:

1. The modest efficacy of dronedarone compared to placebo (for example, EURIDIS and ADONIS with 22-27% reduction in atrial fibrillation recurrence compared to placebo and the 24% reduction in cardiovascular hospitalisation compared to placebo) and the significantly inferior efficacy of dronedarone compared to amiodarone as seen in the DIONYSOS trial.
2. The lack of a significant reduction in mortality for dronedarone over placebo and the significantly increased mortality for patients on dronedarone compared to placebo in the ANDROMEDA study.
3. The limited long term data for dronedarone, especially in relation to safety.
4. The large number of drug interactions with dronedarone that could be difficult to manage in clinical practice and the potential safety consequences.
5. The pro-arrhythmic effects of dronedarone, for example, prolonged PR and QTc intervals compared to placebo, as seen in the EURIDIS, ADONIS and ATHENA studies along with PR and QTc interval prolongation when dronedarone is used with other drugs such as verapamil, propranolol and digoxin.
6. The increased risk of bradycardia and heart failure compared to placebo and therefore the potential for increased mortality given the findings in the ANDROMEDA trial and dronedarone's pro-arrhythmic effects.
7. The lack of a study investigating a lower dose of dronedarone than 400mg twice daily and whether such a dose could be efficacious but potentially have an improved safety profile.
8. The significant increase in hepatic liver enzymes, for example, 12% in the DIONYSOS study, which may be a signal for significant hepatotoxicity when used by patients, especially when on other medications or with concomitant diseases.
9. The lack of clinical trials comparing dronedarone with other treatments for atrial fibrillation, such as beta blockers.
10. The appropriate use of dronedarone with angiotensin converting enzyme inhibitors or angiotensin receptor blockers.
11. Why the product is dosed twice daily when the half life is about 25-30 hours.
12. Any risk minimising activities, including further amendments to the Product Information (PI) or use of the product, which could address the safety concerns of dronedarone if used in the wider population.
13. Any PSURs from the use of dronedarone overseas and whether they address the concerns raised above.
14. If any further clinical trials have been completed but not submitted to the TGA or if there are any further trials currently ongoing with dronedarone. Please identify these studies and if they could address the concerns raised above.
15. Please submit an integrated table of adverse events from all trials comparing dronedarone, placebo and amiodarone at a suitable cut-off, for example, 1%.

The sponsor's responses to the questions are summarised (*in italics*) below along with the Delegate's comments.

Q1: *The sponsor commented that several studies have indicated there is no correlation for existing antiarrhythmic drugs between ECG effects and beneficial clinical outcomes such as death, cardiovascular death and hospitalisation. A recent meta-analysis by Doyle et al indicated that whilst amiodarone was effective for maintaining sinus rhythm compared to placebo, it did not show an improvement with respect to morbidity or mortality.<sup>8</sup> In the DIONYSOS trial, amiodarone was superior to dronedarone in maintaining sinus rhythm, however as already noted, amiodarone does not appear to provide a benefit in terms of morbidity or mortality. In contrast, dronedarone has shown efficacy in prolonging the time to recurrence of AF/AFL in three trials and has also demonstrated a reduction in cardiovascular hospitalisation in the ATHENA trial. Subgroup analyses also showed that dronedarone was beneficial in terms of cardiovascular death and sudden death. Although the ATHENA trial was a placebo controlled trial, it was on top of standard rate control therapies. The sponsor notes that the AFFIRM trial showed that cardiovascular hospitalisation is a strong predictor of death, thus showing the importance of this outcome measure and that the ATHENA trial is the first time an antiarrhythmic agent has shown clinical outcome benefits for AF patients. The sponsor therefore contends that the efficacy of dronedarone is not modest.*

The Delegate commented that the data appear to indicate acceptable efficacy given its beneficial effects on cardiovascular hospitalisation, sudden death and cardiovascular death but the apparent lack of correlation between ECG effects and clinical outcome is unclear.

Q2: *The ATHENA trial did not demonstrate a significant reduction in mortality compared to placebo, however a trend was observed (RR 0.84, 95%CI 0.66, 1.08). The overall mortality from all trials is summarised below noting a similar trend for dronedarone compared to placebo. The active comparator trial, DIONYSOS, also showed fewer deaths on dronedarone although the trial size is too small to be conclusive. Cardiovascular death and sudden death were however reduced in the ATHENA trial. In comparison, the ANDROMEDA study in patients with unstable congestive heart failure (left ventricular dysfunction, shortness of breath on minimal exertion or rest, hospitalised with new or worsening heart failure) showed a significantly increased risk of death, RR 2.13 (95%CI 1.07, 4.25). However there was no evidence of proarrhythmia. The sponsor contends that clinical stability of patients differentiates the two studies with ATHENA having stable outpatients and ANDROMEDA with unstable hospitalised patients for worsening heart failure.*

The Delegate commented that the sponsor has addressed the heart failure mortality risk through a boxed warning in the PI and through an RMP. The mortality data thus far do not indicate an increased risk for AF/AFL patients and a trend to a reduction on dronedarone was seen. However, the increased mortality from the ANDROMEDA study is concerning, given the potential overlap of AF/AFL with heart failure.

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<sup>8</sup> Doyle JF, Ho KM. Benefits and risks of long-term amiodarone therapy for persistent atrial fibrillation: a meta-analysis. *Mayo Clin Proc* 2009; 84: 234-242.

**Table 1 - Summary of analysis of time from randomisation to death from any cause during the on-study period (all randomised and treated patients)**

Studies	Number of patients with endpoint		Relative Risk [95% CI] <sup>a</sup>
	Placebo	Dronedaron 400mg BID	
DRI3550/DAFNE	0 (N=66)	0 (N=76)	No deaths reported
EFC3153/EURIDIS	0 (N=201)	2 (N=411)	Not applicable
EFC4788/ADONIS	5 (N=208)	9 (N=417)	0.794[0.266-2.370]
EFC4508/ERATO	1 (N=89)	1 (N=85)	1.066[0.067-17.046]
EFC5555/ATHENA	139 (N=2311)	116 (N=2293)	0.841[0.657-1.076]
Total AF/AFL Population <sup>b</sup>	145 (N=2875)	128 (N=3282)	0.849[0.668-1.077]

<sup>a</sup> Determined from Cox regression model

<sup>b</sup> Relative risk from Cox model is adjusted on studies

Note: Protocols : DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA

Q3: The sponsor commented that the clinical database for dronedarone is the largest ever conducted for an antiarrhythmic agent for AF/AFL with 8276 subjects of whom 6285 were in the five AF/AFL trials. Total exposure to dronedarone was 4867 subjects with 3410 in the five clinical trials with 1998 treated for up to one year and 425 for up to two years. The sponsor has noted that the amiodarone adverse effects of interest, generally dose-related and reversible, include peripheral neuropathy (0.1-1%), corneal microdeposits ( $\geq 10\%$ ), skin reactions such as photosensitivity ( $\geq 10\%$ ) and slate grey bluish pigmentations of the skin (1-10%), pulmonary toxicity (1-10%), isolated increases in serum transaminases ( $\geq 10\%$ ), acute liver disorders (1-10%) and thyroid disorders which include both hypothyroidism (7%) and hyperthyroidism (1.4%). A table was provided to show the time period for expected amiodarone like reactions and a comparison with the dronedarone database on its adequacy for detecting these events. The sponsor contended that the database is adequate to detect most of these reactions for up to 2 years, given also the mainly common frequency of their occurrence. The actual frequencies reported for dronedarone versus placebo and versus amiodarone indicate they are similar to placebo except for photosensitivity reactions and thyroid effects which were slightly higher on dronedarone, but similar or less than amiodarone. There were no events of peripheral neuropathy in the DIONYSOS study. The RMP will specifically monitor for interstitial lung disease, neuropathy, hepatic reactions and severe skin reactions and pharmacoepidemiology studies are also being conducted.

The Delegate commented that the safety profile appears mostly acceptable based on the data presented, but specific attention should be paid to hepatic reactions, photosensitivity reactions, thyroid disorders, pulmonary disorders and neuropathy long term.

Q4: The drug interaction profile is stated to be similar to amiodarone and the sponsor contended that dronedarone can be safely prescribed to patients taking concomitant medications. The clinical trial program included a large proportion of patients on concomitant medications, including beta blockers, anticoagulants, ACE inhibitors or angiotensin II receptor blockers or diuretics. Adverse events related to interacting drugs were reviewed and did not reveal specific concerns. Specific drugs have been identified that require caution such as CYP3A4 substrates (for example, calcium channel antagonists), statins, sirolimus, tacrolimus, CYP2D6 substrates (for example, beta blockers) and PGP substrates (for example digoxin). A review of the ATHENA study for the primary endpoint of cardiovascular hospitalisation or death by patients taking concomitant medications, showed benefit was maintained except for concomitant statin use. A further analysis for rhabdomyolysis risk showed the risk to be similar to placebo for concomitant statin use. Post-marketing data have not confirmed any new signals of interactions. The proposed PI includes contraindications for strong CYP3A4 inhibitors (for example, ketoconazole and cyclosporine) and

*medicines that could induce torsades de pointes (TdP). Pharmacovigilance plans include: cross-sectional studies of concomitant medication usage and communication plans for prescribers on interacting drugs (PI, Prescriber Information Sheet on interactions, drug interaction alerts in prescribing software and Multaq Information Leaflet for communication from specialists to general practitioners), patients (CMI in the carton and Multaq Patient Card on the carton on drugs) and pharmacists (Pharmacist Information Sheet and drug interaction alerts in dispensing software).*

The Delegate commented that these approaches seem reasonable to highlight the interactions to prescribers, patients and pharmacists but also to help in transferring patients from specialists to general practitioners. There still remain a significant number of interactions for the prescriber and patient to manage. The lack of specific safety signals from the clinical trial program and post-marketing data thus far are reassuring.

*Q5: The sponsor commented that the increases in PR and QTc intervals are related to its pharmacodynamic effects and not a sign of toxicity. Despite the QTc interval prolongation, dronedarone decreases the dispersion of repolarisation between ventricular epicardial and endocardial cells (unlike the proarrhythmic effects of dofetilide), it decreases the “early after depolarisations” which are triggers of torsades de pointes and the effects of dronedarone on repolarisation are not exaggerated at slow heart rates. Only one case of TdP was recorded in the dronedarone clinical program in a patient with prolonged QTc at baseline and severe bradycardia. The risk of TdP is estimated therefore at 0.1%, which is within the population estimate for AF of 0-0.2% and less than observed with sotalol (2.5%). Deaths from cardiac arrhythmia in the ATHENA trial were 1.1% on dronedarone versus 2.1% on placebo and QTc intervals of >500ms in the DIONYSOS trial were 10.9% on dronedarone versus 20.5% on amiodarone. The sponsor proposed to address this matter in the proposed PI with contraindications for QTc intervals of >500ms and combination with TdP inducing medications and a precaution recommending follow-up ECG during treatment.*

The Delegate commented that these data are reassuring but exposure in the clinical setting may alter the risk.

*Q6: Heart rate reduction is claimed to be an important mechanism of action for dronedarone that leads to its clinical benefit, therefore cases were expected with the overall incidence of bradycardia at 3.2% versus 1.3% on placebo and 6.3% on amiodarone. However serious cases were the same as placebo (0.2% each). In the DIONYSOS trial, bradycardia and PR interval prolongation were less on dronedarone than amiodarone (bradycardia 19% on dronedarone versus 29.5% on amiodarone). The proposed PI also includes a contraindication for bradycardia (<50 bpm). Heart failure in the five placebo controlled trials was seen in 11.2% on dronedarone versus 10.9% on placebo. In the ATHENA trial, hospitalisation due to worsening heart failure was lower on dronedarone than placebo. However the ANDROMEDA study showed an increased risk of death on dronedarone in patients with unstable congestive heart failure. The sponsor proposed to address this through a boxed warning in the proposed PI, contraindications for NYHA Class IV or Class II-III heart failure with recent decompensation requiring hospitalisation, communication and education to prescribers, patients and pharmacists (Prescriber Information Sheet, Pharmacist Information Sheet, alerts in prescribing and dispensing software, CMI and patient card insert) and cross-sectional pharmacovigilance studies.*

The Delegate commented that the risk of heart failure in the AF/AFL trials is similar to placebo and the risk of bradycardia whilst higher than on placebo is less than on amiodarone. The measures proposed by the sponsor seem reasonable given the ANDROMEDA study is in a different population, but given AF may overlap with heart failure, then prescribers need to be fully aware of this risk for patients. The overlap of conditions and potential for incipient heart failure are of concern. Patients enrolled into ANDROMEDA were predominantly NYHA Class II (40%) and III

(57%), with 38% having a history of AF/AFL (25% had AF at randomization). In contrast, in ATHENA, 71% of patients had no heart failure, 25% were NYHA Class I or II, and only 4% were Class III with all patients having a history of AF/AFL. Given the high proportion of patients with NYHA Class II and III heart failure in ANDROMEDA with an increased risk of mortality on dronedarone and the potential overlap of AF with heart failure then there is an argument for contraindicating NYHA Class II and III heart failure completely. Although the heart failure patients in ANDROMEDA were unstable, there is a lack of data for NYHA Class II or III stable patients to know how they would be affected. Further information from the 6 month PSUR report may help to address this matter.

*Q7: Doses of 400 mg bd were the lowest dose tested in the clinical trials, but pharmacology studies assessed a dose of 200 mg bd but found no effect on the QTcF interval, therefore this lack of pharmacodynamic effect meant it was not selected for further study. A PK/PD analysis also showed that patients with lower  $C_{trough}$  values had less benefit than those with higher  $C_{trough}$  values.*

The Delegate commented that the pharmacodynamic data indicate a lack of efficacy at a dose of 200 mg bd, however this was not confirmed in a clinical trial nor were other doses investigated such as 300 mg bd.

*Q8: The DIONYSOS trial showed that increases of ALT and/or AST  $\geq 2 \times$  ULN and more than 0.5 x ULN from baseline were 12.9% of patients on dronedarone versus 13.7% on amiodarone. Patients with ALT  $\geq 3 \times$  ULN were 4.4% on dronedarone versus 3.9% on amiodarone. An analysis by level of liver enzyme elevation in the sponsor's response shows similar but slightly higher levels on dronedarone than amiodarone. In the four clinical trials which systemically collected liver function tests, ALT  $\geq 3 \times$  ULN was seen in 2.5% of dronedarone patients versus 2% of placebo patients. Hepatic disorders were also slightly higher on dronedarone (2.9%) versus placebo (2.5%) but serious hepatic disorders were similar. The abovementioned analysis also shows a slightly higher rate on dronedarone versus placebo at 1 year but a similar rate at 2 years. An analysis of first hepatic events by with or without concomitant diseases or medications showed similar results for each subset of patients. A review of the clinical trial program using a definition of ALT  $\geq 3 \times$  ULN and total bilirubin  $\geq 2 \times$  ULN showed a rate of 0.06% (n=2) for placebo, 0.10% (n=4) for dronedarone and 0.65% (n=1) for amiodarone. The four cases on dronedarone were autoimmune hepatitis, cholangitis, pancreatobiliary obstruction due to pancreatic tumour and hepatic ischaemia secondary to transient low cardiac output. Liver disorders will be monitored post-marketing through routine pharmacovigilance, use of special liver injury data collection forms and a nested case-control study using medical records to evaluate liver injury.*

The Delegate commented that liver enzyme elevations remain a concern and the sponsor should consider including a precaution that periodic monitoring of liver function should be undertaken.

*Q9: As no trial had demonstrated a clinical benefit in AF using an antiarrhythmic agent or beta blocker prior to dronedarone, then the ATHENA trial used standard of care as the comparator which included beta blockers, warfarin, etc. The sponsor stated it would be ethically unacceptable to conduct a head to head comparison of beta blocker to dronedarone since beta blockers have been shown to reduce mortality in various conditions associated with AF, for example, hypertension, as patients randomised to dronedarone would have been deprived beta blockers. Therefore the ATHENA study's strategy was to compare to placebo on top of standard of care for all patients. Other antiarrhythmic agents were also not chosen as they have not demonstrated a clinical benefit in terms of cardiovascular hospitalisation or death. The benefits seen in ATHENA for dronedarone were on top of standard of care. A pre-specified sub-group analysis of this result by concomitant beta blocker use showed that the primary endpoint was efficacious in those with or without concomitant therapies, including beta-blockers, digoxin and calcium channel blockers.*



The Delegate commented that the sponsor's comments were noted, including the similar efficacy results in patients with or without concomitant beta blockers.

Q10: *The ANDROMEDA trial had more frequent discontinuations of ACE inhibitors and angiotensin II receptor blockers (ARBs) in the dronedarone group than the placebo group. This was thought to be due to the rise in creatinine seen with dronedarone (due to inhibition of tubular secretion of creatinine) being confused with nephrotoxicity from ACE inhibitors and ARBs. The clinical data indicate a beneficial effect with or without ACE inhibitors / ARBs and the sponsor proposed a PI precaution to explain this effect. Those reporting an increased creatinine were 3.8% on dronedarone versus 1.1% on placebo. Discontinuation of dronedarone leads to a return to normal creatinine values within 10 days, whereas for amiodarone patients the level remained elevated in the DIONYSOS trial.*

The Delegate commented that this precaution seems appropriate.

Q11: *Twice daily dosing was chosen to minimise peak to trough fluctuations in concentrations whilst maximising drug exposure and minimising tablet strength and size. Exposures were 1.1-1.6 fold higher with bd dosing for dronedarone and its metabolite compared to once daily dosing.*

The Delegate commented that the regimen was noted and was the regimen chosen in the clinical trials.

Q12: *The sponsor has made the following changes to the PI: amended indication, boxed warning on heart failure, contraindication for severe renal impairment and further information on ECGs being required for patients on beta-blockers and calcium channel antagonists. An RMP was submitted to the OMSM which noted heart failure, drug interactions and increased serum creatinine as being important areas for risk minimisation. The sponsor provided a summary of the educational tools that will be used as additional risk minimisation activities along with prescribing and dispensing software warnings, information advertisements in general practitioner (GP) focussed journals and a prescriber survey conducted 12 months post commencement of marketing to assess the effectiveness of their risk minimising activities.*

The Delegate commented that these risk minimising activities seem appropriate and have been accepted by OMSM.

Q13: *The first 3 month PSUR period which showed sales to 24,470 patients did not necessitate an amendment to the US PI but identified 112 serious unexpected adverse events (29 of AF/AFL/supraventricular arrhythmia, 20 of congestive heart failure, 7 of VT/VF including two cases of torsades de pointes in patients with advanced structural heart disease and previous ventricular arrhythmias, 5 deaths likely disease related, 2 reports of significant hepatic injury including one fatal hepatitis but possibly related to ischemic origin and 11 cases of INR increases without bleeding that requires further monitoring). Further information will be provided separately in the 6 month PSUR report.*

The Delegate commented that these findings are consistent with the safety profile of dronedarone but the numbers are small at present.

Q14: *There have been nine further trials not submitted to TGA that mostly concern drug interactions. These note an interaction with atorvastatin lower than previously noted for simvastatin, lack of interaction with CYP2C19, erythromycin increases dronedarone by 3.8 fold, an ongoing study with clopidogrel, lack of interaction with metformin but weak potential to inhibit OCT2 renal secretion of creatinine, weak interaction with rosuvastatin, tolerability data from Japan and a food effect.*

The Delegate commented that these are summary findings that have not been confirmed by the TGA but the sponsor claims have been already covered in the PI, although erythromycin does not appear to be specifically mentioned.

Q15: *Tables have been provided at a 1% cut-off, however due to the length, the PI includes a 2% cut-off.*

The Delegate summarised that the sponsor has submitted a comprehensive response to the 15 matters raised by the TGA and ADEC on dronedarone, including PI amendments, an acceptable Risk Management Plan and acceptable risk minimising activities that include educational activities, communication documents and pharmacoepidemiological studies. Since the submission was first considered by ADEC, the drug has also been approved in Europe and 6 months of PSUR data have become available. Concern remains regarding some safety findings, especially heart failure.

The Delegate stated that the submission appears approvable based on the further information and risk management actions made by the sponsor however the advice of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) was requested. In particular, the ACPM was requested to consider the following two questions.

Has the sponsor presented sufficient information to address the concerns of the committee to enable approval?

Should dronedarone be contraindicated completely in NYHA Class II-III heart failure?

The Delegate proposed to register Multaq for the following indication:

*Multaq is an antiarrhythmic drug indicated to reduce the risk of cardiovascular hospitalisation in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors, who are in sinus rhythm or who will be cardioverted, on top of standard therapy (see Clinical Trials)*

The sponsor should address the following issues in their Pre-ACPM response:

- A summary of any further planned clinical studies with dronedarone.
- Provide an explanation on how to reconcile the findings of the ANDROMEDA trial with the ATHENA trial regarding use in patients with heart failure and the proposed PI statements for NYHA Class II and III heart failure patients.

The ACPM, having considered the additional information provided by the Delegate and the sponsor, agreed with the Delegate and recommended approval for the following indication:

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

In making this recommendation the ACPM agreed with the Delegate that the additional information supported a favourable risk benefit ratio for this product. However, the safety risks remain of concern and warrant the full implementation of a robust RMP, including the enabling of prescribers with access to detailed information about the safety and efficacy of dronedarone.

The ACPM recommended that a specific condition of registration should include the implementation of the submitted RMP to the satisfaction of the TGA.

THE ACPM also recommended that changes to the PI/CMI which should be made prior to approval include:

- a boxed warning to clearly notify prescribers of the dangers of inappropriate use in patients with New York Heart Association (NYHA) Class IV and II-III heart failure with recent decompensation requiring hospitalisation or patients with new or worsening heart failure;
- specific information that patients require heart failure assessment and list the types of appropriate assessment; and
- monitoring of liver function in the Precautions section.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Multaq, Dronedaronе Winthrop and Dronedaronе Sanofi film-coated tablets, at a dose of 400 mg twice daily with meals, indicated for:

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

With the following specific conditions applying to these goods:

The implementation in Australia of the dronedarone Risk Management Plan (RMP), dated 19 February 2010, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

## Attachment 1. Product Information

### PRODUCT INFORMATION

#### MULTAQ<sup>®</sup>

##### WARNING: HEART FAILURE

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

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

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

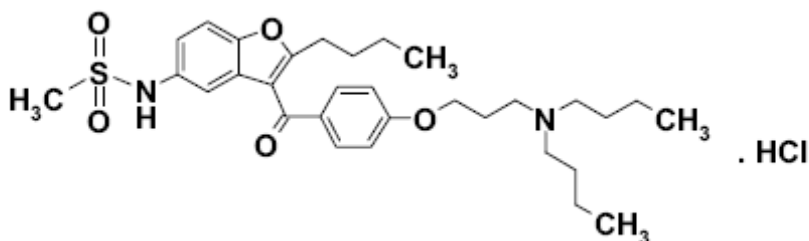
### NAME OF THE MEDICINE

#### Non-proprietary Name

Dronedarone hydrochloride.

#### Chemical Structure

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



#### CAS Number

141625-93-6.

#### Description

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

#### Pharmacology

##### Pharmacodynamics and Mechanism of Action

Dronedarone is an antiarrhythmic agent with electrophysiological properties of all four Vaughan-Williams classes. It is a multiple ion blocker in animal cardiac tissues *in vitro*, inhibiting potassium currents (including IK(Ach), IKur, IKr, IKs (Class III), sodium currents (Class Ib) and the calcium currents (Class IV). It also non-competitively antagonises adrenergic activity (Class II). In animal

models, dronedarone reduces the heart rate. It prolongs Wenckebach cycle length and AH-, PQ-, QT-intervals; with no marked effect or weak increase in on QTc-, HV- and QRS- intervals. It increases effective refractory periods of the atrium, atrio-ventricular node and ventricle with a minimal degree of reverse-use dependency. Dronedarone decreases arterial blood pressure and myocardial contractility (dP/dt max) with no change in left ventricular ejection fraction and reduces myocardial oxygen consumption. Dronedarone has vasodilatory properties affecting the coronary arteries related to the activation of the nitric oxide pathway. Dronedarone displays indirect antiadrenergic effects; it reduces alpha-adrenergic blood pressure response to epinephrine and beta1 and beta2 responses to isoproterenol.

## Pharmacokinetics

### Absorption

Following oral administration under fed conditions, dronedarone is well absorbed (at least 70%). However due to presystemic first pass metabolism, the absolute bioavailability of dronedarone (given with food) is 15%. Concomitant intake of food increases dronedarone bioavailability by on average 2- to 4-fold. Because of presystemic first pass metabolism the absolute bioavailability of dronedarone without food is low, about 4%. It increases to approximately 15% when dronedarone is administered with a high fat meal. After oral administration under fed conditions, peak plasma concentrations of dronedarone and the main circulating active metabolite (N-debutyl metabolite) are reached within 3 to 6 hours. After repeated administration of 400 mg twice daily, steady state is reached within 4 to 8 days of treatment and the mean accumulation ratio for dronedarone ranges from 2.6 to 4.5. The steady state mean dronedarone C<sub>max</sub> is 84–147 ng/ml and the exposure of the main N-debutyl metabolite is similar to that of the parent compound. The pharmacokinetics of dronedarone and its N-debutyl metabolite both deviate moderately from dose proportionality: a 2-fold increase in dose results in an approximate 2.5- to 3.0-fold increase with respect to C<sub>max</sub> and AUC.

### Distribution

The *in vitro* plasma protein binding of dronedarone and its N-debutyl metabolite is > 98% and not saturable. Both compounds bind mainly to albumin. After intravenous (IV) administration the volume of distribution at steady state (V<sub>ss</sub>) ranges from 1200 to 1400 L.

### Metabolism

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

### Excretion

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

### Special Populations

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

### Gender

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

## Elderly

Of the total number of subjects in clinical studies of dronedarone, 73% were 65 years of age and over and 34% were 75 and over. In patients aged 65 years old and above, dronedarone exposures are 23% higher in comparison with patients aged below 65 years.

## Hepatic Impairment

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

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

## Renal Impairment

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

## Clinical Trials

### ATHENA Study

ATHENA was a multicenter, multinational, double blind, and randomized placebo-controlled study of dronedarone in 4628 patients with a recent history of AF/AFL who were in sinus rhythm or who were to be converted to sinus rhythm. The objective of the study was to determine whether dronedarone could delay death from any cause or hospitalization for cardiovascular reasons.

Initially patients were to be  $\geq 70$  years old, or  $< 70$  years old with at least one risk factor (including hypertension, diabetes, prior cerebrovascular accident, left atrial diameter  $\geq 50$  mm or LVEF  $< 0.40$ ). The inclusion criteria were later changed such that patients were to be  $\geq 75$  years old, or  $\geq 70$  years old with at least one risk factor. Patients had to have both AF/AFL and sinus rhythm documented within the previous 6 months. Patients could have been in AF/AFL or in sinus rhythm at the time of randomization, but patients not in sinus rhythm were expected to be either electrically or chemically converted to normal sinus rhythm after anticoagulation. Exclusion criteria included patients with congestive heart failure with NYHA functional class IV, patients with bradycardia ( $< 50$  bpm) and 2<sup>nd</sup> and 3<sup>rd</sup> degree AV block unless treated with a pacemaker. The ATHENA trial also excluded haemodynamically unstable patients and those with permanent AF.

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

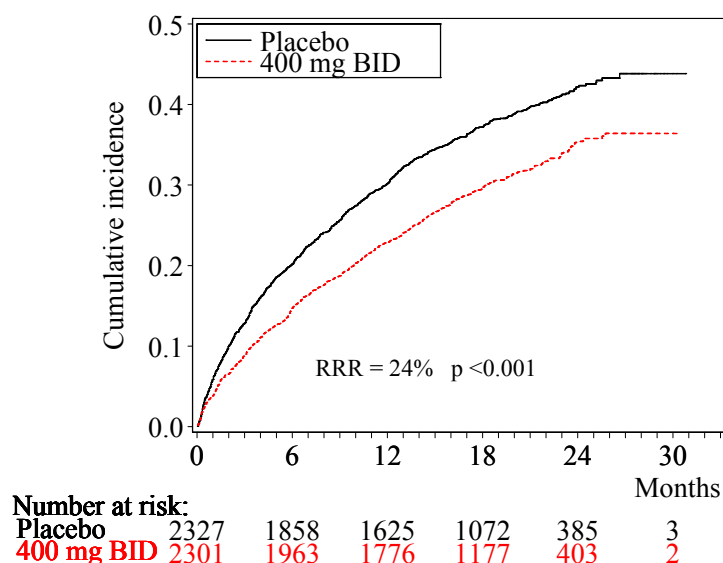
The primary endpoint of the study was the time to first hospitalisation for cardiovascular reasons or death from any cause. Secondary endpoints evaluated were time to death from any cause, time to first hospitalisation for cardiovascular reasons, time to cardiovascular death. In addition, time to sudden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

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

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

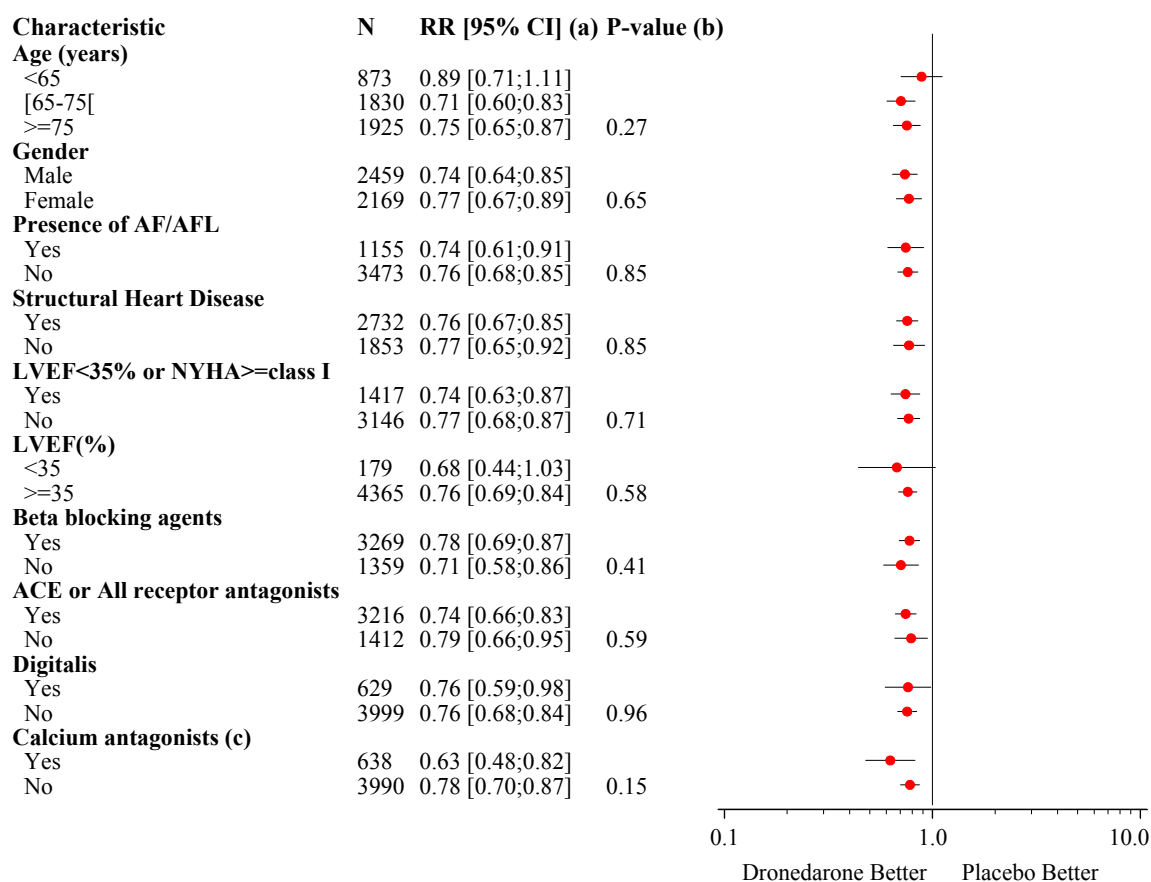
The curves showing the overall event rate are displayed in Figure 1. The event curves separated early and continued to diverge over the 30 month follow-up period.

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



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

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



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

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

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

**Table 1: Incidence of Endpoint Events**

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



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

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

### **EURIDIS, ADONIS, DAFNE, DIONYSOS Studies**

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

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

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

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

In DAFNE where MULTAQ was started before conversion, the median time to AF recurrence, as measured by trans-telephonic electrocardiogram monitoring (TTEM) and 12 lead ECG, was 60 days in

the 400 mg twice daily MULTAQ group, compared to 5 days in the placebo group. MULTAQ 400 mg twice daily lowered by 55% ( $p = 0.001$ ) the risk of first recurrence of AF compared to placebo during the 6 months study period.

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

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

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

### **ERATO Study**

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

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

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

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

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

## Indications

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

## Contraindications

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

Hypersensitivity to dronedarone or to any of the excipients.

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

Bradycardia < 50 bpm.

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

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

QTc Bazett interval  $\geq$  500 msec.

Severe hepatic impairment.

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

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

## Precautions

### Heart failure assessment

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

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

This assessment should include:

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

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

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

NYHA Grading	Symptoms
Class I Asymptomatic	No limitations in normal physical activity
Class II Mild	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina

	pectoris
Class III Moderate	Marked limitation of physical activity. Less than ordinary activity results in symptoms
Class IV Severe	Unable to carry out any physical activity without discomfort. Symptoms present at rest

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

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

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

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

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

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

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

### **Patients with renal impairment**

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

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

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

### **Electrolytes imbalance**

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

### **QT prolongation**

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

### **Bradycardia**

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

### **Patients with galactose intolerance**

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

### **Carcinogenicity and Mutagenicity**

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

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

### **Impairment of Fertility**

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

### **Use in Pregnancy**

Category D

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

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

### **Use in Lactation**

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

### **Use in Elderly**

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

### **Paediatric Use**

There is no experience in children and adolescents.

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

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

### **Interactions with Other Medicines**

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

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

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

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

### **Pharmacodynamic Interactions**

Drugs prolonging the QT interval (inducing Torsade de Pointes)

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

#### **Digoxin**

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

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

#### **Calcium channel blockers**

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

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

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

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

#### **Beta-blockers**

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

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

### **Effects of Other Drugs on Dronedarone**

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

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

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

#### **Grapefruit juice**

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

#### **Calcium channel blockers**

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

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

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

#### **Pantoprazole**

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

### **Effects of Dronedarone on Other Drugs**

#### **Statins**

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

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

#### **Calcium channel blockers**

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

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

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

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

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

#### Digoxin and P-glycoprotein substrates

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

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

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

No interaction was observed between dronedarone and losartan.

#### Theophylline (CYP 1A2 substrate)

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

#### Oral contraceptives

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

### Adverse Effects

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

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

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

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

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



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

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

\* Adverse events considered as related to dronedarone

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

The following CIOMS frequency rating is used, when applicable:

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

#### **Gastrointestinal disorders**

Common: dyspepsia,

#### **Nervous system disorders**

Uncommon: dysgeusia,

Rare: ageusia,

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

Common: pruritus,

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

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

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

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

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

\*\*\*not measured in ATHENA study

## Dosage and Administration

### Adults

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

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

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

Treatment with MULTAQ can be initiated in an outpatient setting.

### Elderly

More than 4500 patients with AF or AFL aged 65 years or above were included in the MULTAQ clinical program (of whom more than 2000 patients were 75 years or older). Although dronedarone exposure was increased in a pharmacokinetic study conducted in healthy subjects, dose adjustments are not considered necessary (see 'PRECAUTIONS, Pharmacology, Special Populations').

### Children

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

### Hepatic impairment

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

### **Renal impairment**

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

### **Overdosage**

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

### **Presentation and Storage Conditions**

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

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

Store below 30°C.

### **Name and Address of the Sponsor**

sanofi-aventis australia Pty Ltd  
12-24 Talavera Road  
Macquarie Park, NSW 2113

### **Poison Schedule of the Medicine**

Prescription Only Medicine (Schedule 4)

### **Date of TGA Approval:**

19<sup>th</sup> July 2010