Dear Sirs

Please accept the following as the Atrial Fibrillation Association stakeholder response to the initial appraisal of dronedarone for AF

Has all the relevant evidence been taken into account?

All the relevant evidence relating directly to the development of dronedarone has been carefully assessed. But evidence relating to the efficacy of other antiarrhythmic agents used for the management of atrial fibrillation has not been assessed other than in a cursory manner. Unmet clinical needs for antiarrhythmic therapy have not been identified. The unique and up-to-date development programme for dronedarone has not been recognised.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The clinical summaries are largely correct, although necessarily some information is omitted. The cost effectiveness studies are not attuned to the potential clinical use of dronedarone. In the setting of recurrent symptomatic atrial fibrillation dronedarone will be used to relieve the symptomatic consequences of recurrent arrhythmia. Quite rightly NICE concludes that the efficacy of dronedarone is of the same order of magnitude as that of flecainide and sotalol, but less effective than amiodarone. However, it is also important to recognise that it's use is considerably less dangerous than that of flecainide, sotalol and amiodarone. Professional guidelines (the writer is also the chairman of he European Society of Cardiology (ESC) Guidelines for Atrial Fibrillation which will be published in September 2010) will continue to place amiodarone as a drug of last resort because of its unacceptable adverse effect profile. Dronedarone will be appropriately positioned according to the evidence base is one of four choices after beta blockade: flecainide, propafenone, sotalol or dronedarone, but before amiodarone. The advice from the ESC will state that the order in which these four drugs should be considered depends on whether antiarrhythmic efficacy, cost efficacy, or safety and is the overriding consideration. Most cardiologists will judge dronedarone to be the safest of the antiarrhythmic drugs.

Should dronedarone not be effective , that is if one or two symptomatic recurrences occur, its use will be terminated since suppression of symptoms is the therapeutic intent for this group of patients. The present cost-efficacy studies do not include this most likely clinical scenario. In any event costs are not likely to be high since only a relatively small proportion of patients in this category will remain on dronedarone for prolonged periods of time. Alternative treatments will then include other antiarrhythmic drugs, catheter ablation or amiodarone as a last resort.

It should be noted that there is evidence in this group of patients (from EURIDIS and ADONIS) that dronedarone may be effective after failure to class 1c antiarrhythmic drugs and sotalol, but there is no evidence in patients who have failed amiodarone. There is a

head to head comparison of amiodarone and dronedarone (DIONYSOS) and arrhythmia recurrence is part of the composite endpoint. Amiodarone was more effective but was also associated with more clinically significant adverse effects, a difference which is minimised by the short term nature of this study. There is no established justification for trying dronedarone after amiodarone failure unless the use of amiodarone is curtailed by adverse effects.

Dronedarone therapy is also envisaged for use in patients with recurrent atrial fibrillation and cardiovascular risk factors. Dronedarone is the only drug which has been investigated in this setting and has been shown to be associated with improved cardiovascular outcomes (ATHENA trial). The primary endpoint of time to all cause mortality or cardiovascular hospitalisation was impressively and significantly reduced in those treated with dronedarone (HR = 0.76). Although this effect was largely driven by reduced cardiovascular hospitalization, all cause mortality was also numerically reduced. Only CV mortality could be expected to be affected by Dronedarone and the lack of effect on cardiovascular mortality was not significant, probably because of the "noise" introduced by deaths from other causes in the elderly population recruited to the ATHENA trial. There was a similar reduction of all cause deaths and cardiovascular deaths in this study. The ATHENA trial design was based on a meta-analysis of EURIDIS and ADONIS data and the trial result was therefore no surprise since it matched very well with the previous meta-analysis.

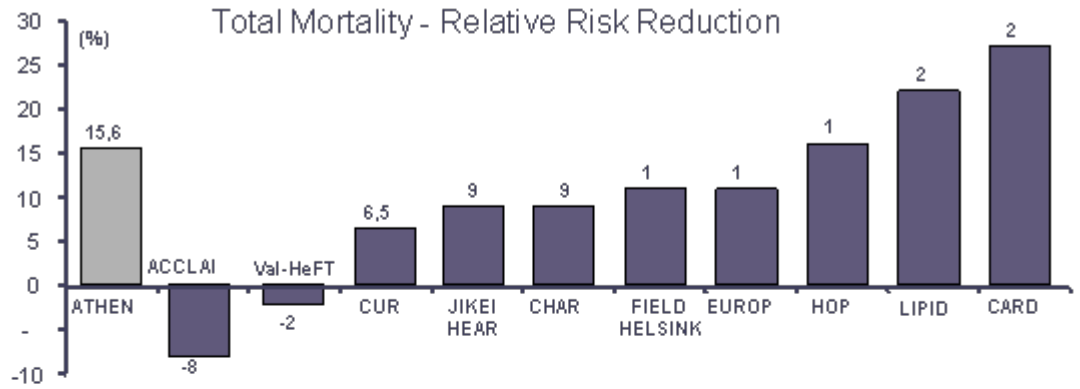
Flecainide, propafenone and sotalol are contraindicated in the majority of patients in this category (because of ischaemic heart disease - flecainide and propafenone, heart failure - sotalol, flecainide and propafenone, or hypertension/hypertrophy ± diuretic use – sotalol). Although amiodarone may have a beneficial effect in this patient group. there is no comparable trial data to support this, and meta-analyses, although of limited value, lend absolutely no support to amiodarone having a similar salutary effect. On the other hand, the ATHENA data are very convincing, and in particular demonstrate that there is little or no likelihood that dronedarone aggravates mortality (upper limit of 95% CI for all cause mortality = 1.08). There is also a very large and long exposure to dronedarone in this trial, which fails to reveal adverse effects of any note. Thus dronedarone stands alone as the only antiarrhythmic drug which has been proven to reduce important cardiovascular outcomes in an AF population at increased risk of cardiovascular events.

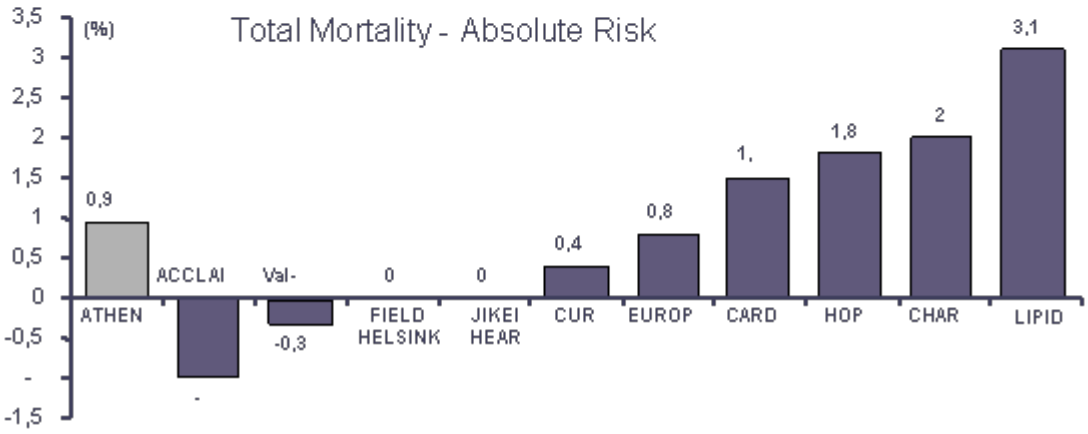
In patients with heart failure, cardiovascular hospitalisation has been readily accepted as an appropriate endpoint in clinical trials. Regulatory authorities have encouraged cardiac electrophysiologists to adopt similar endpoints in antiarrhythmic drug trials for the management of atrial fibrillation, rather than relying on symptom reduction and the prevention or delay of atrial fibrillation recurrence. Dronedarone is the only drug for which this assessment has been made, and the result is very positive.

In patients with cardiovascular risk and recurrent symptomatic atrial fibrillation sotalol, propafenone and flecainide are usually contraindicated, and dronedarone and amiodarone are the only antiarrhythmic agents that are available. Professional guidelines will continue to restrict amiodarone to the drug of last choice because it has an unacceptable side effect profile. Many patients also have specific contraindications to amiodarone and many have tried this drug previously, developed serious and incapacitating complications and must

stop therapy with the drug. For them dronedarone is the only antiarrhythmic which is available.

The effect associated with dronedarone in the ATHENA trial is substantial and comparable to the results of other major trials of agents which are used routinely to prevent significant cardiovascular outcomes. The effects demonstrated with dronedarone are achieved in patients already well treated with other agents used for cardiovascular protection. Please see the annualised relative and absolute risk reductions for morbi-mortality and total mortality rates from such trials in the charts below:





Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The recommendation that “dronedarone is not recommended for treatment of atrial fibrillation” seems to be perverse. Dronedarone is the only drug proven to reduce serious cardiovascular outcomes in patients with cardiovascular risk and it appears to be the most “safe” antiarrhythmic that is available.

The Atrial Fibrillation Association would like the committee to consider the following indications:

1) Dronedarone is recommended after trial of beta-blockade, for treatment of symptomatic atrial fibrillation in patients with recurrent symptomatic atrial fibrillation

Although, as expected at this stage of drug development, there are no head to head trials of dronedarone against other agents in this category – flecainide, propafenone, and sotalol – the clinical expectation, in the full knowledge of the extremely good adverse event profile associated with dronedarone, is that dronedarone is approximately equipotent and much more safe that other antiarrhythmic agents. By unanimous informed clinical academic opinion Amiodarone, the calibrator drug required by European regulators, although more efficacious than dronedarone is also much less safe and must, of course, remain the antiarrhythmic drug of last resort

2) Dronedarone is indicated for patients with cardiovascular risk and recurrent atrial fibrillation (excluding patients with stage IV heart failure or heart failure with recent decompensation).

Dronedarone is the only antiarrhythmic drug which has been shown to effectively reduce cardiovascular outcomes in this patient cohort. It does not cause an increased mortality. Most other antiarrhythmic are contraindicated in this patient group because they are known to be unsafe in patients with frequently associated comorbidities. There is no evidence that amiodarone reduces cardiovascular risk – similar studies such as AF-STAT, AFFIRM show absolutely no evidence that amiodarone reduces the risk of important cardiovascular outcomes. Dronedarone is unique in this regard.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

I do not believe that the present recommendation intends to discriminate against any of the above subgroups of patients but, since most patients with recurrent atrial fibrillation and cardiovascular risk who are likely to benefit substantially from treatment with dronedarone are elderly, the recommendation against dronedarone treatment effectively discriminates against the elderly.

The NICE consultation process, which is based almost entirely on communication via the internet (either to apply for paper forms or to complete the forms entirely on the web), is very difficult or impossible for very many of elderly patients. This also discriminates against this group. The Atrial Fibrillation Association has had numerous complaints to this effect.