Dear Sirs

I write as an Executive Committee Member of the Arrhythmia Alliance (an umbrella organization representing patients and clinicians involved with the treatment of cardiac arrhythmias) regarding the recent Appraisal Consultation Document on dronedarone (Multaq) for atrial fibrillation.

There has not been a new antiarrhythmic drug available in the UK for a quarter of a century: the agents available, while out of patent and therefore cheap to prescribe, are all highly unsatisfactory as none is easy to use, widely safe or tolerable. There is a critical need for a drug that can be prescribed in patients with symptomatic AF, with a high degree of safety and a low incidence of side-effects. The arrhythmia community has long been searching for a benign version of amiodarone, even if it is not quite as effective.

It is regrettable that at its meeting, the appraisal committee did not appear to have the opportunity to be informed by arrhythmia specialists, and consequently may not have fully understood some of the issues regarding antiarrhythmic treatment for atrial fibrillation (AF[FDM1]).

Symptom Control

First of all, antiarrhythmic treatment is generally prescribed for symptom control in patients with recurrent paroxysmal or persistent AF, and this is considered separately from the need for risk reduction. The Consultation Document at times seems to conflate these issues.

In deciding whether to give antiarrhythmic treatment, and which agent to use, the cardiologist takes into account the type, severity, and frequency of symptoms attributable to the arrhythmia. For example, a patient with very infrequent arrhythmia, or with frequent but asymptomatic arrhythmia will rarely be prescribed an antiarrhythmic drug at all. As a result, only a minority of the huge number of patients with a diagnosis of AF are in need of antiarrhythmic treatment. Interestingly, patients are more likely to be symptomatic if they are younger, and have the paroxysmal form of AF (CARAF data, Connolly et al).

For that minority of patients, however, AF episodes can be debilitating and have a severely detrimental effect on quality of life. Not only may they experience palpitation, presyncope, dyspnoea, and profound lethargy during episodes of AF, but they may be debilitated for a period of time *after* each episode has finished. Furthermore (as with conditions such as epilepsy), the uncertainty over when the next episode will be, and how severe or prolonged, hangs over patients and affects their ability to work, plan, etc even during periods of normal rhythm,

In its considerations, the committee compares dronedarone to drugs in class 1c (flecainide and propafenone), sotalol, and amiodarone. The data from EURIDIS and ADONIS have demonstrated that dronedarone is effective when compared to placebo, and those from DIONYSIOS indicate that this efficacy is inferior to that of amiodarone and probably comparable to that of sotalol and flecainide (the data are remarkably similar to historic studies of these agents). These agents cannot, however, be regarded as equivalent alternatives.

- Firstly, the efficacies of antiarrhythmic drugs are not uniform. A drug that halves the number of AF episodes in a cohort of patients will be quite ineffective in some and highly effective in others. Furthermore, a lack of response to one drug in a patient does not necessarily predict lack of response to another. From a mechanistic point of view, sotalol shares a few actions with amiodarone, and virtually none with

flecainide; the same pertains to dronedarone. It would therefore be worth trying dronedarone in patients for whom other agents are ineffective.

- Secondly, cardiovascular safety considerations effectively rule out the use of certain agents in certain patients. Flecainide is contraindicated in those with coronary disease, impaired left ventricular function, or left ventricular hypertrophy. Sotalol carries a propensity to provoke malignant ventricular arrhythmias in a proportion of patients.
- Thirdly, side-effects are a significant problem with sotalol (perhaps a third of patients do not tolerate this drug in an effective dose) and amiodarone (in one study, 40% of patients ultimately discontinued because of noncardiovascular side-effects). Most cardiologists avoid using amiodarone altogether in younger patients as the complications increase with the duration of treatment.
- Finally, amiodarone is difficult to prescribe because of its very long half-life. Even with an accelerated loading regime it only reaches full efficacy after a month or so of treatment, and it takes 2-3 months to come out of the system. During these periods, warfarin dosing is ever-changing and the administration of alternative antiarrhythmic drugs is difficult.

Thus, for a treatment used almost entirely for the reduction of symptoms and improvement in quality of life, safety, tolerability, and "usability" are paramount. In this respect dronedarone appears to be unique.

Risk reduction

As regards risk, the cardiologist considers two factors when treating patients.

- First of all, the risk of stroke, for which the CHADS2 score provides a useful aide-memoire in determining who requires anticoagulation. Those patients currently receive warfarin which is highly effective (though underused as it is a very unsatisfactory drug in many ways).
- Secondly, the combination of AF with other factors puts patients at risk of death and other (non-stroke) cardiovascular morbidity. No antiarrhythmic drug has hitherto been shown to lower this risk and with most agents the risk is actually increased (e.g. the AFFIRM trial and many others). Amiodarone has at best has a neutral effect on risk. Because of concerns in severe heart failure arising from the ANDROMEDA study, the ATHENA study specifically looked at the safety of dronedarone in AF patients with other cardiovascular risk factors. It is remarkable that dronedarone was found not just to be safe in these patients, but that it was associated with a significant lowering of risk of both stroke and other cardiovascular events. This effect was surprisingly large, and though not fully explained probably results from a number of separate actions (e.g. less stroke due to less AF, reduction in ventricular arrhythmias, sympatholytic action).
- We accept that the data are as yet insufficient to result in a recommendation that dronedarone be prescribed in order to reduce stroke and cardiovascular risk. However, it is clear that the safety profile of this drug is unique and this alone makes it essential that cardiologists be permitted to prescribe this drug for symptoms.

Cost-effectiveness

The cost-effectiveness calculations provided by the committee are complex and beyond the scope of this letter. However, some of their premises appear to be flawed in that

- For the reasons given above, dronedarone, class 1c drugs, sotalol, and amiodarone are not directly comparable.
- It is apparent within weeks or at most months (in the case of amiodarone) whether an antiarrhythmic drug is improving symptoms. Thus a prescription for dronedarone will only be continued if (and for so long as), it is effective.
- The cost efficacy calculations should perhaps be based on the premise that dronedarone will be prescribed in a patient for whom "first line" therapies are ineffective, not tolerated, or safe; and *will only be continued* if it proves effective in that patients.
- If dronedarone is used in this manner, those who fail to respond will have to consider amiodarone with all its potential for toxicities, or the far more expensive alternative of catheter ablation of the AV node (with pacemaker implantation) or of the AF substrate.

Summary

There must always be caution in recommending a new drug as first line therapy, especially in view of the difficulties and complexities of antiarrhythmic prescribing. We also accept that dronedarone is somewhat less effective than amiodarone, and seems to be of roughly equal efficacy to class 1c agents and sotalol.

At this stage, we would therefore not see it being initiated in general practice but only by cardiologists. It would be a very useful alternative to class 1c drugs or sotalol, in patients (requiring symptom control) for whom these drugs are contraindicated, or in whom they have been found to be ineffective or poorly tolerated.

Dronedarone is the first agent for a quarter of a century to be licensed for rhythm control in atrial fibrillation, and it does show a remarkable tolerability and safety profile. To completely deny it to our patients as an alternative to other drugs would be a major regressive step.

Yours sincerely

[redacted]

Arrhythmia Alliance

Executive Committee