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29th January 2010

Professor Peter Clark/Ms Nicole Reid,
Chair,
NICE Appraisal Committee for Dronedarone
Level 1A
City Tower
Piccadilly Plaza
Manchester M1 4BD

Dear Professor Clark/Ms Reid,

Re: NICE Appraisal consultation document – Dronedarone for the treatment of atrial fibrillation

As you know Dr Neil Sulke is the nominated HRUK (Heart Rhythm UK) nominated representative to the NICE Appraisal consultation considering Dronedarone. Neil is responding separately to the ACD with a detailed response, and following on from your conversation with him, I am very grateful for the opportunity to respond to the draft document as [redacted] of HRUK.

Firstly let me say that HRUK is very appreciative of the comprehensive analysis undertaken by the Appraisal Committee in looking into the potential role of Dronedarone as an antiarrhythmic drug.

It is our regret that the HRUK clinical representative was unable to attend the appraisal committee meeting in November 2009 and it was our mistake that a substitute who could attend was not arranged.

However, we wish to help by contributing a clinical perspective to help the Appraisal Committee come to a decision on Dronedarone based on, amongst many other relevant factors, as comprehensive an understanding as possible of the potential clinical value of this medication.

We have taken note of the high level of concern by patient organisations regarding the draft consultation document. However, I have been approached, lobbied and cajoled by a very large number of clinicians and clinical experts who are dealing with arrhythmias on a daily basis. It is from this perspective that I

write and believe it very important I represent their views and make available to the committee their feelings.

In essence the clinical view is that Dronedarone would be a useful adjunct to the treatments available for AF. I have tried to summarise the reasoning in the following points:

1. Atrial fibrillation is increasing and the numbers affected by this condition is very large.
2. There is a dramatically increasing rate of referrals to cardiologists, particularly those cardiologists specialising in patients affected by heart rhythm abnormalities.
3. There are relatively few medications available, and their success rate for controlling symptomatic patients with atrial fibrillation is limited (20-40%).
4. The most problematic group of patients with AF to treat is those with symptomatic AF where a rhythm control strategy (endeavouring to maintain sinus rhythm by preventing recurrence of AF) is the preferred option.
5. Many of the medications available have significant risks associated with them (eg Sotalol has a the highest risk among antiarrhythmic drugs for QT prolongation and induction of life threatening ventricular arrhythmia; Flecainide carries a risk of provoking ventricular arrhythmias in patients with ischemic heart disease and in those who undertake reason levels of recreational exercise).
6. Amiodarone has such an unfavourable long term risk profile that correctly it is reserved, according to every set of guidelines from professional expert bodies, to cases where the 'limited' number of conventional medications (beta blockers, sotalol and Class Ic medications) are ineffective.
7. Clinical guidance advises of the use of <u>either</u> Amiodarone <u>or</u> catheter ablation for symptomatic atrial fibrillation refractory to conventional medications.
8. There is an increasing referral rate for expensive interventional therapies (catheter ablation, pacemakers etc).

You will appreciate that most of these concerns relate to **symptomatic** atrial fibrillation. The ACD did refer to both symptomatic and asymptomatic patients. It is central to our clinical approach for the treatment of heart rhythm problems that the differences in management nuances between these two groups are appreciated fully by the appraisal committee. These two groups of patients are managed in importantly different ways. Heart rhythm specialists need more treatment options for patients with symptomatic AF, particularly treatments that are free of serious side-effects. Other approaches (managing thromboembolic risk, treatment and prevention of heart failure) while important in all patients with AF are the prime issues in asymptomatic AF.

The clinical arrhythmia community is, like the Appraisal Committee, intrigued by the findings of ATHENA Study – outcome benefit in the absence of evidence of a powerful antiarrhythmic efficacy. However we are accustomed to clinical trials demonstrating no benefit in 'all cause mortality' or indeed increased mortality, in trials of anti arrhythmic medications known to have powerful anti arrhythmic effects. The benefits of the latter are counteracted by the ability of these drugs to promote life threatening arrhythmias. So, far rhythm experts throughout the world the ATHENA results were not completely unexpected, and are consistent with a hypothesis of moderate benefit not being confounded by cardiac toxicity (the purpose behind the design of a modification to the most effective antiarrhythmic drug having the properties that lead to its toxicity being removed). In other words we see the study confirming the relative safety of dronedarone, encouraging its safe use in patients with symptomatic AF. This sits alongside the evidence from previous studies of modest antiarrhythmic efficacy. Because failure of symptomatic control will inevitably lead to cessation of that particularly strategy, and moving to alternative options the consideration of mortality benefits are not quite as relevant to many of the incremental cost effectiveness models.

Expressed more simply the ability to use a 'relatively' inexpensive medication for relief of symptoms in order to prevent progression to alternative more toxic medications or expensive interventions is a something we would welcome.

Yours sincerely,

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[redacted], Heart Rhythm UK.