

**Comments from the British Society for Heart Failure on the Consultation Document
for the Single Technology Appraisal of
Ivabradine for the Treatment of Chronic Heart Failure**

The consultation documents issued by the STA have identified most of the issues pertinent to advice on the new drug, Ivabradine, which has a licence based on limited data from *post-hoc* sub-set analyses of a single RCT. The recommendations for the usage of the drug are restricted to certain circumstances, and for the patients and the NHS the potential benefits of the drug can only be realised, and will only be cost effective, if the drug is prescribed within certain proscribed circumstances. Current “enthusiasms” for the drug, that are disproportionate to the proven effects of the drug, appear to pose very considerable risks in terms of an escalating drug bill and a risk that other highly efficacious interventions including beta-blockers may not be delivered. There are a number of instances in which we would therefore argue for tighter wording (see below).

The key messages are those of the preliminary recommendations of STA and which are subsequently confirmed in the final recommendations – and hence applicable to the conclusions of the appraisal (under 41.8):

- 1.1 First point - It would helpful to include in the first statement that this drug is for those with systolic dysfunction and an EF of 35% or less (rather than just leaving it as Left ventricular systolic dysfunction or LVSD, which elsewhere the document defines as an EF less than 45%).
- 1.1 Third point – Suggest the wording is modified to ”when given in combination with standard therapy including beta-blocker therapy, ACE inhibitors and aldosterone antagonists, or when beta-blockade therapy is *truly* contraindicated or *truly* not tolerated”. Such wording would be consistent with the wording used around beta-blockers in the CHF 2010 guidance.
- 1.2 Suggest an additional statement is added here saying that Ivabradine should not be initiated during an acute HF admission – although this is self-evident from the existing statement this practice has already emerged and it would be useful to emphasise that this is not current guidance. (It is of note that the prescribing of Ivabradine during acute or unstable heart failure is listed as a contraindication within its current license).
- 1.3 The initial recommendation that Ivabradine is only prescribed following a referral to secondary care has disappeared from the STA final recommendation without any explanation – was this intended? We would argue powerfully for the statement to appear in the final recommendations as an additional bullet point as it does in the

initial recommendations, but argue that it is simplified and clarified (as outlined below in the response to the initial recommendations).

This statement under 1.3 is currently open to interpretation and will lead to widespread potential prescribing of Ivabradine without a robust evidence base. It should be quite explicit that the treatment should be initiated by the Heart Failure Lead, usually a Consultant Cardiologist – the current wording leaves much ambiguity and already there are wider discussions abroad that this could be interpreted as a secondary care nurse going into the community, or a GPSI. Too early or injudicious introduction of Ivabradine will be costly for both patients and the NHS, and would fall without the current economic model and limited evidence basis. The indication for referral to secondary care at this juncture is to ensure heart failure treatment has been truly optimised and to ensure there are not other interventional or other strategies which should be considered – this really needs senior HF and usually consultant cardiology input, as included within the appraised economic model. If this does not happen there is a very real danger that the drug will be used without the current evidence base at considerable expense with no evidence of benefit. We would therefore suggest the wording, which is currently somewhat ambiguous, is changed from the current:

“Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team“ to the following:

“Ivabradine should be initiated by the secondary care heart failure lead”.

The suggested wording is entirely consistent with NICE 2010 CHF guidance and its definition of specialist, though given the numerous interpretations of the word specialist we would suggest it is best avoided in this instance. The cost of a single consultation is modest compared with the potential cost of widespread mis-prescribing of the drug. **We would strongly recommend including this advice.**



Other more general comments:

There are a number of instances throughout the document where the committee refer to Ivabradine as an alternative heart-rate-lowering drug for people who are in sinus rhythm and for whom beta-blockers are not suitable”. This statement suggests 1) that the effect of beta-blockers are through rate lowering alone whereas there is good evidence that there are additional mechanisms for the massive benefit of beta blockers in HF, and 2) that they are equivalent drugs whereas they have different mechanisms of action. This or similar wording is employed in sections 4.1 and 4.4 (in the final table), and it would be helpful if the wording reflected the differences in the drugs and indeed prescribing patterns i.e. beta-blocker prescribing is often limited by a heart rate of 60, whereas Ivabradine should not be initiated if the heart rate were for example 72 at rest.

Although there was no pre-defined comparator with Digoxin within the STA, it would be worth noting that for patients in sinus rhythm and heart failure due to LVSD, already receiving the three first line drugs, there is an alternative therapy, and one which, based on recent *post hoc* sub-set analyses, appears to confer similar benefits to Ivabradine, even though their mechanisms of action are distinct, and which interestingly appear to have a similar impact upon heart rate. Of note it is a well-established therapy for patients with LVSD, and often used for the more unstable patients, and especially amongst those in NYHA III and IV.

Is the population studied typical of the UK population?

This is addressed by the appraisal but arguably has slightly over-stated the difficulty in recruiting patients from within the UK. An alternative explanation for the poor recruitment is that the centres, of excellence, found it difficult to recruit patients from the UK when well treated with conventional drugs including beta-blockers. Certainly there appear to be large differences in age, and ethnic mix between the studied population and the UK population, which have been partially discussed.

We wonder however if it would be useful to flag the licensed terms and contraindications as part of the guidance – for example many potential users seem unaware of the interaction with the P450 cytochrome system (though if there is the guidance for initiation in secondary care this might be less of an issue). This is pertinent to other drug usage such as some antibiotics, but may also be pertinent the widespread genetic variations that are found – given that the studies have been carried out on rather homogenous groups it may be that more widespread variations in handling the drug will be unmasked in the diverse genetic variations of the UK population.

We note discussion around the usage of Ivabradine in the context of resynchronisation – it is worth flagging that many patients who do not tolerate target doses of beta-blockers pre device deployment, are so improved by resynchronisation, that post implantation there is often scope to up-titrate the beta-blockers. In contrast pacemaker dependence is listed under the licence as a contraindication for the prescribing of Ivabradine.

Answers to specific questions:

Has all the relevant evidence been taken into account?

Yes subject to comments above

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

Yes but will only be applicable if prescribing adheres to those patients included in the model – more widespread prescribing would not necessarily be either clinically effective or cost-effective

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

Yes subject to suggested amendments above.