NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Ivabradine for the treatment of chronic heart failure

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Suzanna Hardman

Name of your organisation Nominated by the Royal College of Physicians (London) ***

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? No
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? No
- other? (please specify Chair to the British Society for Heart Failure

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

The condition for which Ivabradine is being considered is Heart Failure (HF) due to Left Ventricular Systolic Dysfunction. Current guidelines, including the 2008 ESC guidance (currently being updated), the NICE 2010 HF partial update and subsequent related Quality Standards (2011) all recommend first line treatment for this patient group should be Beta-blockers combined with an Angiotensin converting enzyme inhibitor (ACEI) since both agents substantially reduce the risk of all cause mortality, and risk of subsequent hospital admissions, which is then associated with deteriorating quality of life. There is now a general consensus that these patients should also receive aldosterone antagonists since when added to beta-blockers and ACEI, in mild moderate and severe HF they further reduce the risk of death or hospitalisation. (An Angiotensin receptor blocker, ARB, may be used in place of an ACEI if the patient is truly intolerant).

There is extensive data available on the extent to which this guidance, which has a very robust evidence base, is implemented both from primary care sources and from data collected for those admitted to hospital (including subsequent readmissions). In both settings the data demonstrate considerable variation in practice depending upon local investment, organisation and utilisation of resources. These variations are best exemplified by the findings of the National Heart Failure Audit Report of 2012. This is based on the analyses of data submitted on 36,504 patient records for the year 2010 to 2011 with just under 70% being diagnosed with HF due to left ventricular systolic dysfunction. The inpatient mortality and subsequent outcomes (including mortality and readmissions projected to 12 months) are predicated by place of care and

specifically access to cardiology with specialist HF support. Key determinants of outcomes subsequent to an index admission include the prescribing of three key drugs namely ACEI, beta-blockers and aldosterone inhibitors at discharge, alongside cardiology follow up, and access to diverse other specialist HF services. The extent to which patients can access these services appears to differ considerably between hospitals, with consequences for subsequent patient survival and well-being. Those patients who might derive particular benefit include the elderly and those with complex co-morbidities including chronic pulmonary disease. Yet these are those least likely to receive appropriate care including beta-blockers, a failing that is often duplicated in primary and community care settings. Thus it is evident from the National Heart Failure Audit that much work remains to be done around improving inpatient care including the prescribing of life modifying drugs, both during and subsequent to hospital admissions.

Against this background there is an intriguing hypothesis that an agent capable of lowering heart rate *per se* might confer benefits for patients with LVSD already receiving conventional treatment.

Whilst there is extensive evidence that a slower heart rate is associated with better outcomes a slower heart rate is also a marker of well being, be that general fitness, or a desirable response to treatment with a beta-blocker and other HF treatments without intrinsic rate slowing properties, alongside diverse other less than fully understood effects. The question arises as to whether lowering heart rate per se confers clinical benefit or not. Of note whilst beta-blockers lower heart rate during treatment the beneficial effects of this group of drugs appear to be substantially related to treatment effects other than just heart rate lowering – and the target of treatment has been to achieve doses prescribed in clinical trails rather than a specific heart rate. Nonetheless if a patient's response to a beta-blocker is a substantial drop in heart rate, this does appear to confer greater benefit than when a more modest heart rate reduction is found.

The development of Ivabradine which acts upon the If channel of the sinus node and so slows the heart rate, has allowed the lowering of heart rate as an intervention in patients with left ventricular systolic dysfunction to be investigated, with randomised placebo controlled trials. Two studies have now been reported Beautiful in 2008 and SHIFT in 2010.

Ivabradine was first used as the active intervention in a randomised controlled trial in patients with stable coronary artery disease and left ventricular systolic dysfunction, and the study designed to explore an effect on a composite primary endpoint of cardiovascular death, admission to hospital for acute myocardial infarction, and admission to hospital for new onset or worsening heart failure. Either Ivabradine, or placebo, was added to standard treatment with beta-blockers, ACEI and aldosterone inhibitors (alongside other agents.) The study did not demonstrate any significant benefit on the composite primary end point. Nor was there any evidence of benefit in terms of the composite end-point, or on cardiovascular death or heart failure admissions, in a pre-specified sub group with heart rates of 70 beats per minute, or higher at randomisation. The authors were however able to conclude that the drug was safe and should be studied further, noting that a sub-group with heart rates above 75 beats per minute might be of greater interest than 70 beats per minute.

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In 2010 the effects of Ivabradine, now explored as a randomised intervention compared against placebo in a group of patients with stable symptomatic heart failure, with an ejection fraction of less than 35%, and a heart rate of 70 bpm or more, who had been hospitalised in the preceding year and were already receiving standard HF treatment (ACEI, beta-blockers and aldosterone antagonists), were reported. The primary end-point was the composite of cardiovascular death or hospital admission for worsening heart failure, with evidence shown of benefit driven largely by heart failure readmissions. There was no difference in all cause mortality between those receiving the active agent and those receiving placebo. The authors, again, addressed the question of heart rate and concluded that greater benefit was evident when the baseline heart rate was above the median for the group studied. Of note this would have included patients with chronic obstructive airways disease, COPD, (accounting for 37% of patients who were not given beta-blockers and in whom it is now recognised that there is especially compelling evidence for prescribing beta-blockers, with mortality benefits in relation to both heart failure and COPD).

Subsequent to the SHIFT publication post-hoc subset analyses have been undertaken of the data and unusually this is the basis of a European, and hence UK, license granted “for patients with chronic stable heart failure due to LVSD, with a heart rate above 75 beats per minute, in combination with standard therapy including beta-blockers or when they were contraindicated or not tolerated”.

By restricting the analyses to the sub-set of patients with heart rates of 75 or above, the manufacturers were able to demonstrate a greater relative risk reduction on the composite primary end point and additional apparent benefits on other secondary end-points including all cause mortality. Of note, as discussed above, the contraindications to beta-blockers in patients with COPD sited when these studies were undertaken no longer pertain. It is also relevant that there were very few patients with HF NYHAIV recruited to SHIFT, and although the license has included this group, even the manufacturer’s advocate caution in this group who many would not consider “stable”. Furthermore, in their conclusions the SHIFT author’s comment that the proportion of elderly patients was low and suggest the data are not generalizable to the overall population with chronic heart failure. Importantly, they also stress that no inference can be drawn about the relative benefits of Ivabradine in the absence of background heart failure treatments including beta-blockers.

In contrast with these judicious caveats the publication of SHIFT (August 2010) was accompanied by an enthusiasm and series of unsupported claims in the popular press that were not matched by the published evidence. This enthusiasm has not abated since. Thus, unusually there may be pressures brought to bear that may drive the prescribing of this drug well beyond the current evidence base. Does this matter? Yes. The early use of Ivabradine before the sometimes time consuming introduction and up-titration of beta-blockers have been exhausted may preclude their later introduction with both a financial cost to the NHS, and a likely mortality cost to the patients in question. Furthermore early over-adoption of the agent may preclude additional much needed clinical trials that would allow the HF community to better understand the true potential of what remains an enormously interesting but as yet largely unproven clinical agent.

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Given the complexities of the issues that now need to be addressed, NICE might wish to explore a recommendation that Ivabradine prescribing is limited to specialist clinics based in secondary care to ensure those with COPD and others labelled as showing "intolerance to beta-blockers" (where there remains a dearth of evidence for Ivabradine) are carefully assessed and wherever possible beta-blockers introduced before Ivabradine is considered. To date the evidence from community based prescribing is that many patients eligible for beta-blockers continue to be denied this intervention that would reduce their risk of dying and hospitalisation. Were overenthusiastic prescribing of Ivabradine to occur instead there would likely be both financial and mortality costs for an especially vulnerable group of patients.

A group of patients in whom it may be particularly difficult to rapidly up-titrate beta-blockers are those with low blood pressures and in recent months, amidst the tide of enthusiasm for Ivabradine, this group has often been cited as a group who may derive particular benefit from Ivabradine. Yet it is of note that Ivabradine is contraindicated in the presence of "severe hypotension (<90/50)". There is a very real concern that if advocated for general prescribing in HF there would be considerable prescribing without the current limited evidence base.

The data, around the use of Ivabradine, is only now beginning to emerge, and the license based on post hoc sub-set analyses only recently granted. To date there are no HF guidelines that incorporate recommendations on the place of this agent in the treatment of HF, but the forthcoming ESC updated HF guidance will include reference to this agent (due to be published shortly). Undoubtedly additional RCTs will be of considerable interest.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of

life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

There is no other agent with pure rate slowing properties with which Ivabradine the subject of this HTA can be compared and to that extent this agent is unique and of considerable interest.

SHIFT explored the use of this agent in patients with LVSD already receiving standard heart failure care including beta-blockade. It is of note that investigators from the UK, across nine centres, all well versed in delivering good heart failure care were collectively only able to recruit a total of 11 patients to the study. I thus have concerns as to how often patients, properly treated with standard agents, will meet the criteria on which the study was based. There do appear to be very few patients who genuinely cannot tolerate more than low dose beta-blockade and for these it may prove a useful agent, though the clinician and patient should together explore the benefits of adding what will often be the 5th or 6th or (for some the 15th or even 20th) drug to their existing medication.

At this juncture, notwithstanding the license, there is little evidence of benefit for patients in the absence of any beta-blockade, in the elderly, and a dearth of evidence for patients in NYHA IV, whilst Ivabradine is contraindicated in unstable heart failure, and in the presence of severe hypotension <90/50, (one of the more common limitations for prescribing or increasing the dose of beta-blockers). It should be avoided where there is evidence of sinus node disease including SA block, or 3rd degree AV block, amongst other conditions.

To date we have little evidence of serious side-effects but this may emerge and particularly if the prescribing is to be extended beyond its use in the two RCTs reported to date.

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

There has been considerable recent interest in the heart rate of UK HF populations, but it is of note that heart rate has not to date been the target for intervention and arguably we still lack robust evidence that treating heart rate *per se* results in meaningful improved clinical outcomes, though this may yet emerge. Undoubtedly the emerging evidence is of considerable interest, but now needs further exploration with RCTS to test the hypotheses that emerge from the sub-set analyses conducted in the two major trials to date.

Historically the National HF audit has not recorded heart rate though for some patients it is possible that this data could be obtained. However, since many patients who are eligible for beta-blockers have not yet been prescribed this agent at the time of discharge, and for most others these agents have not been optimally up-titrated such data, whilst of interest should be used in the first instance to improve practice around the prescribing of beta-blockade, and other standard disease modulating medications which with patient improvement may favourably temper heart rate.

Ivabradine is being assessed through a Single Technology Appraisal, for use in chronic heart failure, at an early stage in its development. Whilst this novel therapeutic agent is of enormous potential interest it is only with additional clinical trial data that its place in the treatment of HF can be fully understood.

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Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Provided guidance reflects current limited evidence there should not be excessive costs associated with its careful introduction. NICE could ensure the prescribing of the drug were not abused if it were to recommend its introduction in the first instance through specialist secondary care clinics, rather than widespread less carefully supervised availability of the drug.