

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: Professor Martin R Cowie

Name of your organisation: British Cardiovascular Society

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- 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.)?
- other? (please specify)

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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.

There is general agreement on best practice in terms of diagnosis and treatment of heart failure, with an update to the NICE guideline being issued in 2010 (CG108). National audit has shown some variation in practice across the country, and readmission data also show quite marked variation from one area to another, suggesting uptake of the guideline advice is variable, or that implementation is difficult.

The standard treatment of heart failure due to LV systolic dysfunction is with an ACE inhibitor and beta-blocker, with some diuretic if needed. These 'process measures' are now included in the GMS QOF targets and the national (secondary care) HF audit, and the Quality Standards for HF.

This technology – ivabradine – is indicated for a (smallish) subgroup of patients with heart failure due to LV systolic dysfunction who are in sinus rhythm and with a heart rate of 75 beats per minute or above (EU license), despite best 'conventional' therapy with ACE inhibitor and beta-blocker (if tolerated). This patient population is a subgroup of those that were enrolled in the pivotal trial, SHIFT (that included patients with heart rate of 70 beats per minute and above) due to the regulator wishing to be sure the patient group had all-cause mortality benefit, rather than the somewhat softer primary endpoint of combined CV mortality and heart failure hospitalisation. In the licensed group, the benefits in terms of all-cause mortality, heart failure mortality and heart failure hospitalisation were striking. This rather unusual step by the

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regulator was backed up by subgroup analysis that showed that there were no clinical or demographic effect modifiers of the benefit of ivabradine compared to placebo, other than heart rate at entry, where the beneficial effect was greater with a higher initial heart rate. This is in keeping with the pharmacodynamics of the agent, with a greater heart rate lowering effect when the resting heart rate is higher.

The technology has few adverse effects (bradycardia, phosphenes, and perhaps a signal to slightly increased risk of atrial fibrillation) and compared to most other heart failure therapies does not affect blood pressure or renal function. This implies that the technology could be applied in either primary or secondary care, although one would wish to be reassured that the patient was already on optimal therapy with an ACE inhibitor and beta-blocker.

Concern has been raised in the clinical community that less informed practitioners might not try beta-blockade as aggressively as they should, opting to try heart rate lowering with ivabradine first. This is not how the drug is being positioned by the manufacturer (to the best of my knowledge) or in new guidelines from professional associations. The technology is viewed as being of use once the patient has been treated with a beta-blocker to as high a dose as is tolerated (up to the maximal dose used in randomised trials). Guidance would have to be given to this point.

The technology has been available in the EU, including UK, for 5 or so years for the treatment of angina, but it has only recently been licensed for use in chronic heart failure.

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

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

As mentioned in section above, my only major concern about the use of this technology is that ivabradine be viewed as an 'easy beta-blocker' robbing patients of the benefits of that therapy. The usage should be as in the randomised trial i.e. on top of optimised 'conventional' therapy with ACE inhibitor and beta-blocker.

Identifying indicated patients should not be difficult: in sinus rhythm, with chronic heart failure and LV systolic dysfunction, on optimised ACE inhibitor and beta-blocker dose (if tolerated) and with a heart rate of at least 75 beats per minute. The heart rate can easily be determined by clinical examination after 5 minutes rest, or confirmed on an ECG, both of which are standard parts of a heart failure clinical assessment.

The generalisability of the pivotal trial, SHIFT, results to the UK has sometimes been questioned due to the small number of UK patients in the study. As the UK principal investigator I have insight into this issue, which applied to many commercial trials being conducted in the UK at that time. NIHR has recognised the poor performance, and has put in place many measures to increase recruitment to such trials for the future. The clinical and demographic characteristics of the patients in SHIFT are very similar to UK heart failure patients, except that the average age was low 60s, and not mid70s: but, again, this is typical for randomised trials recruiting from specialist centres. Subgroup analysis suggests no effect modification by age, and if relative benefit is maintained the absolute benefit will be even larger.

Health care utilisation patterns do differ from country to country, and I would like to see details of this from the trial to ensure any health economic arguments are sound when applied to the UK population. I presume the manufacturer will be providing this information to the Advisory Panel.

The outcomes assessed in the trial, and in the analyses provided to the licensing body, are 'hard' including total mortality, CV mortality, HF deaths, HF hospitalisations, total hospitalisations, as well as quality of life and patient reported outcomes (unusual for a HF trial) using both generic and disease-specific instruments. This should enable more robust cost-effectiveness analyses than is often the case.

As for side-effects, please see section above. The drug has been available for the treatment of angina for some years and no additional adverse reactions have come to light. Bradycardia is not surprising as a side-effect for this agent, and led to withdrawal of therapy in only around 2% of individuals in the trial. Phosphenes (flashing lights) are rare and resolves with lowering the dose or stopping the drug. Compared to most drugs used for the treatment of heart failure, this agent appears much simpler and safer to use in a wide range of circumstances. This is also my own clinical experience.

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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.

Assessing generalisability to the UK heart failure population might be helped by looking at the National HF Audit and local published audits. All of these should be identified easily on systematic searching of the published literature.

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)?

I do not think that the introduction of this technology to the indicated group of patients would put much constraint on the health service. The technology is only applicable to a minority of patients, no complex procedures are needed to identify such patients, and monitoring after introduction of such therapy is straightforward and typical for a patient with the severe condition of chronic heart failure. Minimal extra education would be provided, but could be given as part of usual multidisciplinary team education, as outlined in the NICE CHF guideline, quality standards etc.

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