NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Ivabradine for treating chronic heart failure

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Servier Laboratories	**Section 1.3:** '***Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team; following initiation, dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.***' **Proposed amendment:** *'Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Following initiation, dose titration, monitoring and continuation may be carried out by a healthcare professional experienced in the treatment of heart failure, under the guidance of a heart failure specialist.*' **Justification:** The manufacturer wishes to endorse the current wording that ivabradine should be initiated by a heart failure specialist. Following initiation, the manufacturer proposes a slight alteration to the wording of the second sentence for the following reasons: Firstly, the proposed wording is in keeping with the SPC recommendation, "the treating physician should be experienced in the management of chronic heart failure." Secondly, The National Hearty Failure Audit suggests that approximately half of HF patients in England & Wales do not have access to a heart failure specialist nurse (1). These patients are also very unlikely to have access to a 'GPwSI' – a GP with a formal qualification to treat heart failure. The NICE guidance in its current form would require primary care services to incur the additional cost of referring these patients to a hospital outpatient clinic for monitoring. This may be regarded as being at odds with the ongoing drive towards efficiency savings in the NHS. To overcome this issue it is important that dose titration and monitoring requirements for ivabradine are not bracketed with initiation, and may be carried out by a healthcare professional experienced in the management of heart failure. This is appropriate for two reasons: (i) GPs in the UK are accustomed to the continuous maintenance of ivabradine for its indication in angina, for which it has been available in the UK over the last six years. The approach for ivabradine in heart failure is similar.	Comment noted. The Committee discussed how ivabradine should be prescribed after initiation by a heart failure specialist. It agreed that the initial recommendation in 1.3 of the ACD should remain the same in the FAD; that is: *'Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team; following initiation, dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.'*

Consultee	Comment	Response
	(ii) GPs routinely maintain other heart failure treatments, including beta-blockers, which have similar clinical considerations. Indeed this is reflected in NICE CG108 where it is stated that beta-blockers should be introduced in a 'start low, go slow' manner and heart rate, blood pressure and clinical status assessed after each titration. Healthcare professionals should already therefore be routinely measuring pulse in the majority of patients with heart failure.	
	Section 3.8: ***'The treatment effect of ivabradine was not statistically significant for cardiovascular mortality and was borderline statistically significant for heart failure, unlike in the clinical trial in which they were significant'.*** **Proposed amendment:** '*The treatment effect of ivabradine did not appear to be statistically significant for cardiovascular mortality or heart failure mortality in the multivariable regression models developed for the cost effectiveness model. However, the presence of an interaction term in these equations (treatment*baseline heart rate) must be taken into account. Including a treatment interaction term in a regression model distorts the value of the treatment effect and the associated statistical significance. The treatment effect of ivabradine is borderline significant on CV mortality and significant for heart failure mortality if the treatment interaction term is excluded from the multivariable regression model. Given that the risk equations used to inform the economic model were based on data from the entire SHIfT cohort (heart rate ≥70 bpm), this is consistent with the results reported for the main clinical analyses in SHIfT (heart rate ≥70 bpm).* *However the treatment effect of ivabradine was found to increase with increasing baseline heart rate. In the licensed population (heart rate ≥75 bpm) ivabradine was associated with a significant reduction in both heart failure mortality and cardiovascular mortality. The multivariable analyses, which include a treatment interaction term and thereby take into account the change in the treatment effect with increasing baseline heart rate, also predict that the efficacy of ivabradine improves with increasing heart rate*.'	Comment noted. Section 3.38 of the FAD has been amended to '*The treatment effect of ivabradine in the regression analysis was not statistically significant for cardiovascular mortality (p=0.38) and was borderline statistically significant (p=0.06) for heart failure mortality, (although these results had been statistically significant for the population covered by the marketing authorization only).* The evidence section of the FAD is only a brief summary of the evidence submitted by the manufacturer and does not aim to give a full account of all the clinical and cost effectiveness analyses undertaken.

Consultee	Comment	Response
	<u>Justification:</u> Firstly the statistical significance of the treatment covariate should not be interpreted in isolation due to the presence of the interaction effect in the regression model. The inclusion of treatment interaction with heart rate changes the value of the regression coefficient and distorts the statistical significance of the coefficient term. This explains why the statistical significance of the treatment effect differs substantially from the clinical data. It is also noted that whilst the primary treatment term was not statistically significant in these regression equations (and would not have been expected to be) the treatment interaction term was significant in both hospitalisation and heart failure mortality risk equations and borderline significant in the CV mortality risk equation. Secondly, the risk equations have been developed from data from the whole SHIfT cohort (patients with a heart rate ≥70 bpm). A non-significant treatment effect on CV mortality in this population would be consistent with the clinical analyses undertaken on the overall SHIfT dataset. The economic analysis does not therefore contrast with the clinical results as suggested.	Comment noted.
	<u>Section 4.9:</u> ***'The Committee concluded that given the results of these exploratory analyses, the effectiveness of ivabradine with increasing beta-blocker doses is uncertain'.*** **<u>Section 4.14:</u>** ***'The Committee concluded that the additional treatment effect of ivabradine was uncertain compared with the effect of beta-blocker doses'.*** **<u>Summary of Appraisal Committee's key conclusions (p.40):</u>** *'**the effectiveness of ivabradine with increasing beta-blocker doses is uncertain**'* **<u>Proposed Amendment:</u>** *'The multivariable risk equations developed for the economic analysis suggest that the relative treatment effect of ivabradine would not be expected to differ for patients on target dose therapy (given the same baseline heart rate) and that it is baseline heart rate which is the key driver of the treatment benefit of ivabradine. Nonetheless, the Committee concluded that given the results of exploratory univariable analyses, the effectiveness of ivabradine with increasing beta-blocker doses is uncertain*.'	Comment noted. Sections 4.9 (now section 4.7 in the FAD) and 4.14 refer to the Committee's considerations. The proposed statement does not reflect the Committee's discussions and conclusions on the uncertainty of the treatment effect of ivabradine with increasing beta-blocker doses.

Consultee	Comment	Response
	Justification: These statements suggest that the treatment effect of ivabradine at higher doses of beta-blockers is uncertain. The manufacturer wishes to comment that any uncertainty in SHIfT regarding the treatment effect of ivabradine at target dose beta-blockade exists because patients were not randomised to target dose beta-blocker therapy. On balance, the available evidence suggests that the ivabradine treatment effect was *not* reduced by beta-blockade once differences in baseline heart rate (and other patient characteristics) were taken into account. The identified statements do not appear to take this evidence into account. It is acknowledged that univariable analyses indicate that the ivabradine treatment effect reduces with increasing beta-blocker dose. However, simple univariable analyses 'throw away' a lot of information available from the SHIfT dataset and in isolation may provide a misleading picture of the potential treatment effect of ivabradine, particularly given the low underlying clinical event rate in this population and potential patient heterogeneity. Critically, analyses based on observed event rates in a non-randomised subgroup are unable to take into account potential imbalances in patient characteristics between the trial arms which may confound event rates and estimates of the treatment effect. In SHIfT there was evidence of an imbalance in patient characteristics in patients on target dose beta-blocker therapy (patients on ivabradine were older, more likely to be in a higher NYHA class and were more likely to have ischaemic heart disease compared to patients in the standard care arm). In these circumstances a multivariable analysis, which takes into account differences in baseline characteristics, can offer a more robust estimate of the treatment effect. The multivariable risk equations developed for the economic analysis use all the available information from SHIfT (n=6505) to predict outcomes for the patients with a heart rate ≥75 bpm and on target dose beta-blockade. These analyses suggest that the ivabradine treatment effect was modified by baseline heart rate but showed no evidence that the treatment effect was modified by other key baseline characteristics, including beta-blocker dose, once differences in baseline heart rate had been taken into account. Whilst some uncertainty may exist with regard to the ivabradine treatment effect in patients on target dose beta-blockade, on balance SHIfT data indicates that the treatment effect of ivabradine does not diminish with increasing beta-blocker dose when evidence is analysed using multivariable regression techniques that take into account differences in patient baseline characteristics.	

Consultee	Comment	Response
	Section 4.15: ***'Overall the Committee considered the effectiveness of ivabradine in the subgroup of patients with a resting heart rate of 75 bpm or more derived from the SHIFT trial, the generalisability of the trial to UK clinical practice and the position of ivabradine in the treatment pathway of chronic heart failure (that is after optimisation on standard care therapy with ACE inhibitors, beta-blockers and aldosterone antagonists)'*** **Proposed amendment:** '*Overall the Committee considered the effectiveness of ivabradine in the subgroup of patients with a resting heart rate of 75 bpm or more derived from the SHIFT trial, the generalisability of the trial to UK clinical practice and the position of ivabradine in the treatment pathway of chronic heart failure (that is after optimisation on standard care therapy with ACE inhibitors, beta-blockers and aldosterone antagonists)to be clear*' **Justification:** The manufacturer is querying whether the statement requires a judgement that the effectiveness/ generalisability/ positioning are e.g. satisfactory or clear.	The Committee considered the statement to be clear and requires no change.
	Section 4.15: '***It noted that ivabradine plus standard care was more effective and cost less than standard care'*** **Proposed amendment:** '*It noted that ivabradine plus standard care was more effective and cost more than standard care*.' **Justification:** Ivabradine is expected to improve patient outcomes (mortality and quality of life) and reduce hospitalisation costs but, overall, ivabradine would be expected to result in higher costs than standard care alone.	Comment noted. Section 4.18 of the FAD has been amended accordingly.
Department of Health	The Department of Health confirmed that they had no substantive comment to make regarding this consultation.	Comment noted.
South Asian Health Foundation	We are impressed and content with the ACD now and have no further amendments or additions to make to the draft.	Comment noted.

Consultee	Comment	Response
British Society for 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 emphasize 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).	Comments noted. Sections 1.1 and 4.13 of the FAD have been amended to reflect that ivabradine is recommended for people with a left ventricular ejection fraction of 35% or less. The Committee agreed that the wording of the recommendation is clear that ivabradine should not be prescribed for unstable and acute heart failure. Section 1.1 of the FAD has been updated to state that ivabradine is recommended for stable chronic heart failure and section 1.2 also recommends that people should be stabilised on their current standard therapies before initiation of ivabradine. Section 4.14 of the FAD states the Committee heard from the clinical specialists that a heart failure specialist in secondary care with access to a multidisciplinary team should initiate ivabradine. However, the Committee discussed the emergence of increasing heart failure expertise outside secondary care. It noted that the NICE clinical guideline 108 on Chronic heart failure defined a specialist as a physician with a subspecialty interest in the management of heart failure and who lead a specialist multidisciplinary heart failure team of professionals with appropriate competencies from primary and secondary care. Based on this, the Committee concluded that its original recommendation in section 1.3 should remain unchanged

Consultee	Comment	Response
	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 optimized 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.** [redacted]	Comment noted.

Consultee	Comment	Response
	Other more general comments: There are a number of instances throughout the document where the committee refers 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.	Comment noted. Section 4.7 of the FAD has been amended to reflect that beta-blockers are known to have additional effects beyond their heart-rate-lowering properties.
	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.	Comment noted. The Committee discussed whether digoxin should have been included as a comparator. But it noted that digoxin was not included in the scope for this appraisal and there was no evidence to support its benefit in this population. Therefore the Committee agreed that considering digoxin as a comparator to ivabradine was beyond the scope of this appraisal. Section 4.11 of the FAD has been amended to reflect this discussion
	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.	Comment noted. However, the Committee considered that section 1.3 of the FAD should remain unchanged in line with the definition of a specialist in the NICE Clinical Guideline 108 for Chronic heart failure.

Consultee	Comment	Response
	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.	Comment noted. Section 4.12 of the FAD has been amended to reflect that pacemaker dependence is listed as a contraindication for prescribing ivabradine as stated in the summary of product characteristics of ivabradine. Comment noted Comment noted Comment noted.
Royal College of Physicians	The RCP wishes to endorse the comments submitted by the British Society for Heart Failure (BSH) to this ACD consultation	Comment noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Clinical Specialist	I fully endorse the recommendations in your provisional guidance, and think them clinically sensible and cautious. They will lead to the evidence-based use of ivabradine, without leading to any less usage of beta-blockade. I particularly endorse the recommendation that those with expertise in heart failure will assess the patient prior to the drug being prescribed, but up titration can be performed by a GP with a special interest or a heart failure nurse specialist. The report's assessment of cost-effectiveness also appears very sensible, and reflects the good value of money of this drug in the correct patients. I would like to thank the committee for its handling of these issues, and in particular the sensible way it has dealt with the feedback on the reports from the invited clinical experts. I am very pleased that patients in England will be able to have access to this drug on the NHS.	Comment noted.

Comments received from commentators

Commentator	Comment	Response
BMJ - Technology Assessment Group	1. In point 3.24 it is stated that "***the risk equations were adjusted for baseline heart rate to predict estimates for the population covered by the marketing authorisation with a heart rate of 75 bpm or more"*** this is not strictly true as the regression equations for NYHA classification were not adjusted for heart rate. 2. Point 3.38 states that "***The treatment effect of ivabradine was not statistically significant for cardiovascular mortality and was borderline statistically significant for heart failure, unlike in the clinical trial in which they were significant."*** As pointed out by the manufacturer in the factual accuracy check, this is not strictly true as the regression equations used in the economic model are based on an analysis of the whole trial population, in which the treatment effect of ivabradine on CV mortality was not statistically significant. To clarify, it is probably best to reword this sentence to make it clear that "the treatment effect of ivabradine was not statistically significant for cardiovascular mortality...., unlike the clinical analysis of the licensed population in which they were significant."	Comment noted. Section 3.24 of the FAD has been amended accordingly. Section 3.38 of the FAD has been amended to '*The treatment effect of ivabradine in the regression analysis was not statistically significant for cardiovascular mortality (p=0.38) and was borderline statistically significant (p=0.06) for heart failure mortality, (although these results had been statistically significant for the population covered by the marketing authorization only).*

Commentator	Comment	Response
Commissioning Support Appraisals Service	We are in agreement with the recommendations in the ACD to recommend ivabradine for this indication as on the basis of the evidence considered it is likely that this treatment can be considered clinically and cost effective in real life clinical practice for the sub-group of patients specified in the ACD. • **Ivabradine is an add-on therapy to standard care.** Ivabradine is proposed as an add-on therapy for the treatment of chronic heart failure in patients in sinus rhythm who are receiving standard care, for whom beta-blockers are contraindicated or who are receiving beta-blockers at maximally tolerated doses and who have a resting heart rate of 75 bpm or more. • **Ivabradine reduced rates of cardiovascular death in a sub group of patients with a resting heart rate of 75 bpm or more.** In the SHIFT trial the rate of cardiovascular death or hospital admission for worsening heart failure (primary composite endpoint) in a subgroup analysis of patients with a resting heart rate of ≥75 bpm was statistically and clinically significant with ivabradine. • **There were limitations to the quality of the research**. The manufacturer submitted effectiveness data based on the results of one well-designed and well-conducted international RCT. However, effectiveness in the population for which the manufacturer has marketing authorisation is based on the analysis of a subgroup (participants with a resting heart rate of 75 bpm or more (n=4,150)) identified retrospectively. Although no relevant baseline differences between the ivabradine and placebo groups were identified, the results should be interpreted with caution as this resting heart rate was not a stratification factor at randomisation. • The effectiveness of ivabradine in some patient populations is uncertain. In the SHIFT trial only 26% of patients received the recommended dose of beta-blockers. There is uncertainty around the benefit of ivabradine plus standard care for patients with a resting heart rate of 75 bpm or more and who are receiving at least 25% of the recommended dose of beta-blockers. Ivabradine should only be initiated after four weeks of optimal standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists. The effectiveness of ivabradine in people with NYHA class IV heart failure is uncertain due to small patient numbers.	Comments noted.

Commentator	Comment	Response
	• **Only patients with an ejection fraction of 35% or lower were included in the SHIFT trial.** Consideration should be given to whether only patients with an ejection fraction of 35% or lower should be considered for treatment with ivabradine. • **The results from the SHIFT trial are generalisable to the UK population**. The Appraisal Committee and Evidence Review Group concluded that the results were robust and generalisable to the UK population despite the fact that participants in the SHIFT trial were younger and had more severe heart failure than the UK population, and that there were few UK participants. • **Ivabradine is cost effective compared to treatments usually funded in the NHS, but is a costly alternative to standard care.** Although there were some uncertainties regarding the economic model, the Appraisal Committee concluded that the manufacturer's ICER estimate of approximately £8,500 per QALY was realistic. Based on manufacturers estimates a commissioner could expect to be asked to fund treatment for 66 patients per 100,000 population with ivabradine per year, which would equate to a cost of about £2,778.60 per month per 100,000 population or £33,343.20 per year per 100,000 population in addition to the cost of standard care.	Comments noted.
NHS Devon, Plymouth and Torbay	We are in agreement with the recommendations in the ACD to recommend ivabradine for this indication as on the basis of the evidence considered it is likely that this treatment can be considered clinically and cost effective in real life clinical practice for the sub-group of patients specified in the ACD. • **Ivabradine is an add-on therapy to standard care.** Ivabradine is proposed as an add-on therapy for the treatment of chronic heart failure in patients in sinus rhythm who are receiving standard care, for whom beta-blockers are contraindicated or who are receiving beta-blockers at maximally tolerated doses and who have a resting heart rate of 75 bpm or more. • **Ivabradine reduced rates of cardiovascular death in a sub group of patients with a resting heart rate of 75 bpm or more.** In the SHIFT trial the rate of cardiovascular death or hospital admission for worsening heart failure (primary composite endpoint) in a subgroup analysis of patients with a resting heart rate of ≥75 bpm was statistically and clinically significant with ivabradine.	Comments noted.

Commentator	Comment	Response
	• **There were limitations to the quality of the research**. The manufacturer submitted effectiveness data based on the results of one well-designed and well-conducted international RCT. However, effectiveness in the population for which the manufacturer has marketing authorisation is based on the analysis of a subgroup (participants with a resting heart rate of 75 bpm or more (n=4,150)) identified retrospectively. Although no relevant baseline differences between the ivabradine and placebo groups were identified, the results should be interpreted with caution as this resting heart rate was not a stratification factor at randomisation. • The effectiveness of ivabradine in some patient populations is uncertain. In the SHIFT trial only 26% of patients received the recommended dose of beta-blockers. There is uncertainty around the benefit of ivabradine plus standard care for patients with a resting heart rate of 75 bpm or more and who are receiving at least 25% of the recommended dose of beta-blockers. Ivabradine should only be initiated after four weeks of optimal standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists. The effectiveness of ivabradine in people with NYHA class IV heart failure is uncertain due to small patient numbers. • **Only patients with an ejection fraction of 35% or lower were included in the SHIFT trial.** Consideration should be given to whether only patients with an ejection fraction of 35% or lower should be considered for treatment with ivabradine. • **The results from the SHIFT trial are generalisable to the UK population**. The Appraisal Committee and Evidence Review Group concluded that the results were robust and generalisable to the UK population despite the fact that participants in the SHIFT trial were younger and had more severe heart failure than the UK population, and that there were few UK participants. • **Ivabradine is cost effective compared to treatments usually funded in the NHS, but is a costly alternative to standard care.** Although there were some uncertainties regarding the economic model, the Appraisal Committee concluded that the manufacturer's ICER estimate of approximately £8,500 per QALY was realistic. Based on manufacturers estimates a commissioner could expect to be asked to fund treatment for 66 patients per 100,000 population with ivabradine per year, which would equate to a cost of about £2,778.60 per month per 100,000 population or £33,343.20 per year per 100,000 population in addition to the cost of standard care.	Comments noted.

Commentator	Comment	Response
National Clinical Guideline Centre	The data implied that adding ivabradine has a desirable effect on the morbidity and mortality in patients with heart failure due to left ventricular systolic dysfunction whose heart rate was over 70-75 bpm, either because they were not on beta-blockers due to contra-indication or due to intolerance; or because the patient were on beta-blockers but the dose could not be up-titrated further (usually due to low BP). The report recognises that the main impact came from treatment of patients on no beta-blockers or on low doses of beta-blockers. This is a very important observation.	Comment noted.
	Based on this and on one of the important recommendations of CG 108, we are keen to emphasise: a. That there is no evidence of a comparison between beta-blockers and ivabradine in heart failure (the manufacturer made a comment that the effect of beta-blocker on heart failure is due to slowing down of the heart which is partly true but not entirely, as we know several BB were not as effective and we have CCB that slow the heart and are contra-indicated in heart failure). Thus while ivabradine could be added to the treatment of patients with HF whose HR WAS 70-75 BPM OR ABOVE, we could not transform the sentence into ivabradine can be given as alternative first line therapy as there is no evidence for that at all.	Comment noted. Section 4.9, 4.21 and 1.2 of the FAD states that *'The clinical specialists all agreed that ivabradine is an additional therapy for a subset of people with chronic heart failure who are in sinus rhythm, and not as a replacement for the recommended standard therapies. The Committee concluded that ivabradine should be initiated only after standard treatment with ACE inhibitors, beta-blockers and aldosterone antagonists has been optimised.'*
	• The practitioner and the patient are alerted, alongside the recommendation from this TA, to the main recommendation that challenged the past practice of assuming the presence of contra-indications to BB in certain groups who were thus prevented from deriving the benefits of BB therapy. These include the elderly, those with non-reversible COPD, those with diabetes mellitus, those with peripheral vascular disease and those with erectile dysfunction.	Comment noted. Section 4.10 of the FAD has been amended to recognise that these groups of people should receive beta-blockers in line with the NICE Clinical Guideline 108 on Chronic heart failure.

Commentator	Comment	Response
	The health economic assessment made several assumptions that need to be challenged: a. It assumed that 50% of the HF hospitalisations in the UK will be under cardiology care, this is not correct. Audit data suggests no more than 30% at most are cared for in cardiology wards. This may or may not affect the calculations. b. Although the mean age of the patients in the trial and the sub-study was not higher than 60 years, for some reason the health economic study was based on a mean age of patients admitted at 78 years?	Comment noted. This is an assumption made by the manufacturer in the economic model. Based on this comment, the figure from the Audit data would reduce the estimated cost of hospitalisation. It has already been noted in the FAD that most of the assumptions used in the model were pragmatic and biased towards ivabradine. The mean age of the patients in the base case model was the same as the clinical trial – 60 years, while a scenario analysis based on a UK representative heart failure cohort with a mean age of 78 years was explored by the manufacturer.
	While the advent of Ivabradine in the treatment of heart failure due to left ventricular systolic dysfunction is a very important and welcome development, it would be fair to stress that its position is mainly as an add on agent in patients who are otherwise optimally treated, and for the few who have an absolute contra-indication to beta-blockers and whose heart rate is over 75 bpm. There is a statement towards the end of the report saying that ivabradine is the only non-surgical addition to the therapy beyond what is recommended in the guidelines. I am afraid this is inaccurate: a. While NICE rejected an application by the makers of eplerenone to re-consider its position following the publication of EMPHASIS-HF in November 2010; it remains true that had the GDG been allowed in May 2010 to consider the findings of EMPHASIS-HF then the algorithm for therapy would have reverted to what the GDG originally proposed in January 2010 (namely that the second line of therapy be an aldosterone antagonist), and that these agents could be given to patients in NYHA II. b. If by using non-surgical, the authors of the report did not mean non-invasive, then one has to also add that beyond the guidelines there is another important publication called RAFT study that altered the European guidelines for advanced pacing to include some patients with NYHA class II, provided they fulfilled stringent ECG criteria (QRS duration >150 msec and LBBB).	Comment noted. The Committee considerations and recommendations in the ACD and FAD of this appraisal clearly define standard therapy to include ACE inhibitors, beta-blockers and aldosterone antagonists. See sections 1.1, 1.2, 4.9 and 4.21 of the FAD.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1	I concur with the Committee's preliminary recommendation subsequent to review of the evidence base and following consideration of the clinical and cost effectiveness. I acknowledge the Committee concluded that the results of the SHIFT trial are generalisable to the UK population despite subtle differences however, the Committee's position on the effectiveness of Ivabradine in patients who have not received full recommended doses of Beta-Blockers, who have NYHA Class IV HF or have an ejection fraction of 35% or higher would be appreciated.	Comment noted. The Committee concluded that Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists; or when beta-blocker therapy is contraindicated or not tolerated (as specified in the marketing authorisation). See sections 1.1 and 1.2 of the FAD The Committee was unable to make recommendations on the use of ivabradine in people with an ejection fraction of 35% or higher because there was no evidence to support this recommendation.
NHS Professional	1	Could you please clarify the term heart failure specialist? Could this be a GPSI or HFSN or do you mean just a Heart Failure Consultant? I personally feel that if the criteria are met in 1.1 and 1.2 then it could be started by a GPSI or experienced HFSN in consultation with the MDT.	The recommendation in section 1.3of the FAD is based on the definition of specialist in the NICE Clinical Guideline 108 which is *'a physician with a subspecialty interest in the management of heart failure and who leads a specialist multidisciplinary heart failure team of professionals with appropriate competencies from primary and secondary care.'*

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.