Paragraph to which the comment relates	Description of proposed amendment	Justification for amendment
Paragraph 1.3 states, '***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.***'	*'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.'*	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. (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.

Paragraph to which the comment relates	Description of proposed amendment	Justification for amendment
Paragraph 3.38 states, ***'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'.***	'*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*.'	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.

Paragraph to which the comment relates	Description of proposed amendment	Justification for amendment
Paragraph 4.9 states, **'*The Committee concluded that given the results of these exploratory analyses, the effectiveness of ivabradine with increasing beta-blocker doses is uncertain'.*** Paragraph 4.14 states, ***'The Committee concluded that the additional treatment effect of ivabradine was uncertain compared with the effect of beta-blocker doses'.*** Summary of Appraisal Committee's key conclusions (p.40) states, '**the effectiveness of ivabradine with increasing beta-blocker doses is uncertain**'	**'***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*.'	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

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		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.
Paragraph 4.15 states, '***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)***'	'*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*'	The manufacturer is querying whether the statement requires a judgement that the effectiveness/ generalisability/ positioning are e.g. satisfactory or clear.
Paragraph 4.15 states, '***It noted that ivabradine plus standard care was more effective and cost less than standard care'***	'*It noted that ivabradine plus standard care was more effective and cost more than standard care*.'	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.

Reference List

(1) McDonagh T, Cleland J, Dargie H *et al.* National Heart Failure Audit report April 2010 - March 2011 (2012)