Ivabradine for the treatment of chronic heart failure
ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 11/39

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
49	Table 11 amended; unpublished data deleted.
77	Text around half-cycle correction has been amended.
82	The following sentence has been added to the second paragraph "The manufacturer uses the generalised ordered logistic regression, which is a special type of logistic regression model that relaxes the assumption of proportional odds."
84	The text directly after Box 7 has been amended to outline that Kaplan-Meier data from the full population of SHIfT have been used.
90/91	The paragraph beginning on page 90 and continuing on page 91 has been updated to refer to the treatment effect of ivabradine and beta-blockade rather than the significance of the treatment effect. In addition, it has been made clearer that the regression analysis was calculated using patient data from the full population of SHIfT.
93	Text around the significance of the treatment effect of ivabradine and beta-blockade amended.
122	The 95% confidence interval used in the manufacturer's sensitivity analysis has been corrected and the reason for uncertainty clarified.
123	Text around the use of parametric equations for the within-trial period in the base case has been removed. In addition, text around the significance of the treatment covariate has been clarified.

Table 1. Comparison of beta-blocker dosage in SHIfT versus in UK clinical practice

Beta-blocker dose	**SHIfT[33]** Baseline	**Community heart failure clinic audit[34] [a]**		
		Baseline (N = 2,211)	4 months (N = 1,309)	12 months (N = 910)
None	11%	42%	19%	14%
Low dose	40%	29%	40%	36%
Moderate dose	26%	23%	27%	34%
Target dose	23%	7%	13%	19%

Table reproduced from MS: Table 30, page 104.

[a] It should be noted that the community heart failure clinic audit specified a target dose of 400 mg for metoprolol compared with 200 mg recommended by the ESC,[36] which could result in an underestimation of the number patients achieving target dose.

Note: The manufacturer also presented data from an unpublished study, which, due to the unpublished nature of the data, the ERG has chosen not to present here.

The ERG considers that the manufacturer made every effort to ensure that, in SHIfT, established heart failure therapies were given at optimal doses and in accordance with guidelines.[19;58] The ERG also considers that the potential effect of variation in beta-blocker dose achieved on the clinical effect of ivabradine warrants further investigation, and discusses this area in more detail in Section 4.3.4.

Blinding

Patients and investigators were blinded to treatment group allocation. In addition, the placebo tablets matched the ivabradine tablets in taste and appearance. The CHMP noted a potential issue with maintenance of blinding in that patients and investigators may have been able to attribute the observed reduction in heart rate to treatment with ivabradine (mean heart rate reduction of about 15 bpm in ivabradine group vs about 5 bpm in the placebo group).[36] The CHMP went on to highlight that "reduced heart rates (up to 15 bpm) were observed in 16% to 20% of the placebo patients whereas up to 14% to 18% of the ivabradine patients had a reduction less than 5 bpm". The ERG considers that the key outcomes assessed in SHIfT are objective outcomes and thus are unlikely to be influenced by the patient or the investigator.

Outcomes assessed

As noted in Section **Error! Reference source not found.**, the pre-specified primary outcome in SHIfT[33] was a composite of first event of hospitalisation for worsening heart failure or cardiovascular mortality. The individual components of the primary outcome were assessed as pre-specified secondary outcomes.

Table 2. Philips[92] checklist

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated
S2:Statement of scope/perspective	NICE scope was followed and addressed adequately; the manufacturer was requested to model the licensed population with ≥75 bpm. The ERG notes that the manufacturer has also assessed cost-effectiveness in a variety of relevant patient subgroups including beta-blocker usage.
S3: Rationale for structure	The ERG notes that the manufacturer justified the structure of the model they adopted based on previous publications of related technology appraisals. The ERG considers the model structure to be appropriate and well constructed. However, the use of individual patient level data whilst improving accuracy also impedes running time.
S4: Structural assumptions	The structural assumptions were transparent, and any bias was likely to be against ivabradine. In addition, a number of scenario and sensitivity analysis were undertaken to test the robustness of the different assumptions
S5: Strategies/comparators	All relevant comparators were evaluated and the optimisation of standard care was emphasised.
S6: Model type	Correct, cost-utility analysis
S7: Time horizon	Lifetime is in accordance with NICE methods guide.[91] Shorter time horizons have been used in sensitivity analysis
S8: Disease states/pathways	The ERG agrees with the pathways/health states modelled
S9: Cycle length	The ERG considers one month to be a reasonable cycle length to capture the consequences of model events. Half-cycle correction was included for on-going costs and effects
Data	
D1: Data identification	Data were taken from the whole population of the SHIfT trial. Where external data were used, it was systematically sourced, clearly described and justified by the manufacturer
D2: Premodel data analysis	Pre-model data analysis predominantly consisted of regression analyses which were systematically developed and rigorously assessed by experts in the disease area.
D2a: Baseline data	Baseline data were taken from the SHIfT trial. Conversion of yearly rates to quarterly probabilities was conducted using standard formulae. A half-cycle correction was included for health benefits despite the short cycle length.
D2b: Treatment effects	Treatment effects for each outcome were estimated from the regression equations for that outcome, data from both treatment arms were used to develop the relative treatment effect inline with current guidance.[93] Extrapolation of treatment effects is clearly described and justified. Alternative assumptions on extrapolating methods and treatment effect generated from the SHIfT trial analysis were used in sensitivity analysis
D2d: Quality of life weights (utilities)	Derived from a SHIfT sub-study – PRO-SHIfT, which is well described. The PRO-SHIfT study report and the PRO-SHIfT full publication were provided

- mixed regression.

Parametric regression involves fitting a parametric distribution to the observed data (e.g. the exponential) and developing a regression equation with covariates that predict the parameter values of the chosen distribution.

Logistic regression models (proportional odds models) are a technique used to assess the impact of covariates on categorical data. Essentially, a separate regression equation is developed assessing the impact of covariates on each category and the results of each analysis pooled to give the overall result. This model relies on the assumption that the relationship between any two outcome categorisations is the same (the proportional odds assumption). The manufacturer uses the generalised ordered logistic regression, which is a special type of logistic regression model that relaxes the assumption of proportional odds.

Poisson regression is a regression methodology used to estimate count data (e.g. number of hospitalisations). The logarithm of the count data is modelled with a standard linear regression equation.

Mixed regression is a technique capable of accounting for datasets of repeated observations over time. A mixed regression model accounts for both fixed and random effects on the dependent variable. Fixed effects parameters (e.g. population characteristics) are the same each time they are collected, whereas, random effects parameters are sample dependent.

Further details of statistical terms and concepts are provided in the glossary on pg**Error! Bookmark not defined.**.

Mortality

The manufacturer's model considered both cardiovascular and non-cardiovascular mortality. Estimates of non-cardiovascular mortality were taken from interim UK life tables[(94)] in preference to data from the SHIfT trial.[(33)] The manufacturer states that data from UK life tables, as opposed to data from the SHIfT trial, were used to inform non-cardiovascular mortality because UK life tables provided a larger UK-specific dataset. Furthermore, treatment with ivabradine plus standard care was assumed to have no effect on non-cardiovascular mortality. However, as part of the clarification process, the ERG requested that the manufacturer provide a sensitivity analysis that used non-cardiovascular mortality from the SHIfT trial. In response to this request, the manufacturer provided a univariate sensitivity analysis that used "a non-cardiovascular mortality endpoint adjusted for patient baseline characteristics" (Manufacturer's clarification response pg 21). The impact of this sensitivity analysis was to increase the base case ICER by £1,079. The ERG notes that the risk of non-cardiovascular death is higher in SHIfT than in UK life tables. Therefore, patients in each arm of the model are less likely to survive and experience the benefit of treatment, resulting in an increased ICER for ivabradine (the more effective treatment). However, the ERG accepts the manufacturer's

Box 1. Manufacturer's rationale for using parametric regressions to estimate cardiovascular and heart failure mortality risks in the "within trial" period

It is recognised that in general the most reliable estimate of the patient survival in the "within-trial" period may be obtained from the observed data, a parametric regression has been used in this study to:

- Provide the relative treatment effect of ivabradine and permit specific exploration of the interaction between treatment and baseline heart rate evidenced in SHIfT;
- Provide cost-effectiveness results relevant to the licensed indication (patients with a baseline heart rate ≥75 bpm);
- Provide an estimate of the natural history of heart failure (underlying baseline risk of mortality without ivabradine) and explore differences in the underlying baseline mortality risk due to patient heterogeneity and to permit subgroup analyses;
- Extrapolate SHIfT estimates beyond the SHIfT study period.

The ERG notes that the incremental cost-effectiveness ratio (ICER) obtained using the observed Kaplan-Meier data for the "within trial" period was £794 more than the base case ICER. However, the ERG notes that Kaplan-Meier data from the full population of SHIfT (heart rate ≥ 70 bpm) are used and that these data are unadjusted for heart rate; estimates based on Kaplan-Meier data for the full population of SHIfT may underestimate the effect of ivabradine in the licensed population.

Cardiovascular regression equation

A full description of the process undertaken by the manufacturer to develop the cardiovascular regression equation is provided in Section 6.3.1 of the MS. To summarise, the manufacturer:

1. considered the fit of a range of parametric distributions (see below);
2. compiled a list of potential covariates based on the SHIfT trial protocol, a previously published heart failure risk equation[95] and expert clinical advice;
3. examined the relationship between continuous variables and cardiovascular mortality to ensure any relationship between these variables was accurately represented (i.e., checked whether the relationship was linear, quadratic, cubic and/or centred on the mean);
4. checked the categorisation of binary and categorical variables to ensure appropriate categorisation;
5. used a backwards selection process, validated by a forward selection process to develop the regression equation;
6. assessed the correlation of all included variables and tested any correlated variables for collinearity;
7. assessed the significance of the interaction between the treatment covariate and variables with prior clinical evidence of treatment effect modification;
8. refined the regression equation using steps 5 and 6 in conjunction with assessment of model fit (log likelihood test) and expert clinical opinion.

The final cardiovascular regression equation indicates that female gender, treatment with lipid medications, lower systolic blood pressure, an increase in LVEF of at least 4% (from a baseline LVEF of 26%), beta-blockade at ≥50% target dose and an increase in serum sodium levels (an increase in serum sodium levels indicates the reduction of fluid retention) are individually associated with a statistically significant ($p < 0.05$) reduction in the risk of cardiovascular mortality. Whereas, treatment with ivabradine, an increase in LVEF of less than 4% (from a baseline of 26%) and beta-blockade at <50% target dose are associated with a statistically non-significant ($p > 0.1$) reduction in the risk of cardiovascular mortality. Furthermore, there is evidence that the interaction of treatment and resting heart rate is associated with further reduction in the risk of cardiovascular mortality ($0.05 < p < 0.1$).

Regarding variables that are associated with an increase in the risk of cardiovascular mortality (i.e., those with positive coefficients), the following covariates exhibited a statistically significant ($p < 0.05$) effect on the overall risk of cardiovascular mortality:

- treatment with aldosterone;
- digitalis use;
- loop diuretics (dose/kg/day);
- worsening disease (as classified by NYHA class);
- heart failure of longer duration;
- increasing heart rate (bpm),
- increasing age (years);
- history of stroke;
- decrease in serum potassium (a decrease in serum potassium is a common consequence of the use of diuretics for fluid retention).

In the MS, the manufacturer noted that the use of particular heart failure medications was associated with poorer outcomes, which was contrary to clinical expectations. A particular example was the use of aldosterone antagonists. However, the manufacturer proposed that as "aldosterone was not recommended in a heart failure indication at the time of the SHIfT trial it is likely that patients taking these medications were of poorer health than the average SHIfT patient, and this effect, rather than the true effect of aldosterone use, was captured". Following consultation with clinical experts, the ERG agrees with the manufacturer that this finding may be because aldosterone was not recommended in heart failure during recruitment for the SHIfT trial.

The ERG considers it important to note that the manufacturer's regression analysis (based on the whole population of SHIfT) suggests that beta-blocker therapy of at least 50% of target dose is associated with a statistically significant reduction in the risk of cardiovascular mortality. However, treatment with ivabradine (over and above adjustment of treatment effect for heart rate) is associated with a non-significant reduction in the risk of cardiovascular mortality (Table 25). Furthermore, the

ERG notes that the treatment effect of ivabradine estimated by the regression analysis is less favourable than that estimated by the clinical analysis of the licensed population (Table 26). The variation in estimated treatment effect may be a result of the adjustment for patient characteristics in the regression analysis that are not accounted for in the clinical analysis. However, the ERG notes that the treatment effect estimated by the regression analysis may be lower because the regression equation is likely to under-predict the risk of cardiovascular mortality. Thus, the potential for ivabradine to reduce the risk of cardiovascular mortality is restricted. However, the under-prediction of cardiovascular mortality risk could also be expected to affect the estimated effect of the optimisation of beta-blocker therapy. Therefore, the ERG considers that evidence from the manufacturer's regression analysis further supports the manufacturer's assertion of the importance of optimising beta-blocker therapy ahead of treatment with ivabradine.

Table 3. The relative effect of treatment with ivabradine plus standard care versus standard care on the risk of cardiovascular mortality

Analysis	HR
Parametric regression analysis carried out for the manufacturer's model	0.90
Clinical analysis[33]	0.83
Abbreviation used in table: HR, hazard ratio.	

Heart failure mortality regression equation

As discussed above, cardiovascular mortality was disaggregated into heart failure mortality and non-heart failure cardiovascular mortality. Therefore, a separate regression equation was developed for heart failure mortality based on the patient population of the SHIfT trial.[33] The development details of the parametric regression equation for heart failure mortality and the final heart failure mortality regression equation are not provided in the MS. However, the manufacturer does indicate that the development of the regression equation for heart failure mortality was undertaken using the same methodology as for the cardiovascular mortality regression equation. The final regression equation for total heart failure mortality and the covariates that were included are presented in Table 27.

Table 4. The final regression equation for heart failure mortality (reproduced from the manufacturer's model)

Description	HR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment effect	0.7798	–0.2487	0.1304	0.0560	–0.50	0.01
Digitalis use	1.5609	0.4453	0.1341	0.0010	0.18	0.71
Loop diuretic (dose/kg/day)	1.1836	0.1685	0.0449	0.0000	0.08	0.26
Lipid medications	0.7610	–0.2731	0.1274	0.0320	–0.52	–0.02
Systolic BP[a]	0.9747	–0.0256	0.0044	0.0000	–0.03	–0.02
NYHA III (vs II)	1.3166	0.2751	0.1351	0.0420	0.01	0.54
NYHA IV (vs II)	2.4133	0.8810	0.2961	0.0030	0.30	1.46

- increasing heart rate (bpm);
- increasing age (years).

Based on advice from clinical advisors, the ERG considers that the regression equation for heart failure mortality is clinically plausible.

The ERG considers it important to highlight that the manufacturer's regression analysis suggests that beta-blocker therapy of any level is associated with a statistically significant reduction in the risk of heart failure mortality. By contrast, ivabradine treatment (over and above the modifying effect of heart rate) is associated with a risk reduction that is of borderline significance. Moreover, the treatment effect of ivabradine estimated by the regression equations is lower than that estimated by the clinical analysis of the licensed population (Table 28). The difference in the magnitude of treatment effect may be a result of the adjustment for patient characteristics in the regression equation not accounted for in the clinical analysis. However, the ERG notes that the under-prediction of ivabradine treatment effect may also be because the regression equation is likely to under-predict the risk of heart failure mortality. Consequently, the potential for ivabradine to reduce the risk of heart failure mortality is restricted. However, the under-prediction of heart failure mortality risk could also be expected to affect the treatment effect of beta-blockade. Therefore, the ERG considers it important to emphasise the importance of the manufacturer's assertion that beta-blocker therapy should be optimisation ahead of treatment with ivabradine.

Table 5. The relative effect of treatment with ivabradine plus standard care versus standard care on the risk of heart failure mortality

Analysis	**HR**
Parametric regression analysis carried out for the manufacturer's model	0.78
Clinical analysis[33]	0.61
Abbreviation used in table: HR, hazard ratio.	

Implementation of the risk of cardiovascular mortality into the economic model

In order to implement the estimates of cardiovascular (or heart failure) mortality risk, the manufacturer calculated the survival function S(t) for each of the parametric regression equations implemented in the model as follows:

- Gompertz: $S(t) = \exp\{(-\lambda t)p^{-1}(\exp(pt)-1)\}$;
- Weibull: $S(t) = \exp\{(-\lambda t)p\}$;
- exponential: $S(t) = \exp\{-\lambda t\}$.

Where: t = time; λ = location parameter; p = shape parameter. For details of how the location and shape parameters were calculated from the regression equations, see **Error! Reference source not found.**.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG was satisfied with the estimates obtained from the manufacturer's model. Moreover, the sensitivity and subgroup analyses carried out by the manufacturer provided sufficient assessment of any areas of uncertainty.

5.4 Conclusions of the cost effectiveness section

Overall, the ERG is satisfied that the model developed by the manufacturer to assess the relative cost-effectiveness of the addition of ivabradine to standard care is robust. Recommended methods for the estimation and extrapolation of survival have been followed.[93] In addition methodological recommendations for the assessment and extrapolation of relative treatment effect have been adhered to.[91;93] Furthermore, the ERG notes that all outcomes of interest have been captured either explicitly (e.g. cardiovascular mortality) or implicitly (e.g. adverse events).

The manufacturer carried out extensive sensitivity analysis on key parameters and structural assumptions which revealed that the model results are relatively insensitive to the use of alternative parameters and assumptions. Moreover, some of the manufacturer's key base case assumptions are conservative (i.e. favour treatment with standard care alone), particularly:

- the use of the entire SHIfT population to develop regression equations for the prediction of outcomes and relative treatment effects;
- the assumption of a linear relationship between baseline resting heart rate and cardiovascular mortality;
- the choice of a Gompertz distribution for parametric regression of cardiovascular mortality;
- the use of a regression equation unadjusted for patient baseline characteristics to predict the distribution of patients across NYHA classes.

Sensitivity analysis around the relative effect (hazard ratio [HR]) of treatment on the risk of cardiovascular mortality was the only analysis observed to have a large impact on model results. Variation of the HR between the lower and upper boundaries of the estimated 95% confidence interval of 0.80 and 1.03 (mean estimate was 0.94) resulted in ICERs of £5,655 and £40,638, respectively. However, the ERG notes that the sensitivity of the model to this variation may be a reflection of the uncertainty around treatment effect on cardiovascular mortality risk. The regression analysis (based on the full population of SHIfT) estimated that the effect of ivabradine treatment on the risk of cardiovascular mortality was statistically non-significant. Furthermore, the uncertainty estimated around this treatment effect is higher when regression analysis is based on the full rather

than the licensed population of the SHIfT trial (95% CI: 0.80 to 1.03 for full population vs 95% CI: 0.72 to 0.97 for licensed population) (MS; pg 131).

The ERG notes that not all of the manufacturer's structural assumptions favoured treatment with standard care alone, particularly:

- the absence of age adjustment beyond baseline;
- the assumptions around the extrapolation of NYHA distribution;

The absence of age adjustment for health related quality of life (HRQoL) gains beyond baseline was a structural assumption that favoured ivabradine. However, the ERG notes that the impact of age adjustment was minimal (increased the ICER by £216). Furthermore, the ERG notes that the use of individual patient-level data to calculate the base case ICER, meant that the model had to be re-run each cycle to propagate the adjustment for age throughout the model time horizon. Therefore, the ERG accepts the exclusion of age adjustment from the base case analysis on the grounds of computational expediency.

The base case assumptions around the extrapolation of NYHA distribution favoured ivabradine. However, the ERG considers these assumptions to be reasonable based on evidence of improvement in NYHA classification from SHIfT (see Section **Error! Reference source not found.**).

The ERG notes that the manufacturer constructed the economic model to enable examination of the relative cost effectiveness of adding ivabradine to standard care in various subgroups. Following results from exploratory analyses carried out in the clinical section of this report (Section 4.3.4), the ERG was particularly interested in the results for patients grouped by different levels of beta-blocker dose. The ERG notes that the regression analyses carried out by the manufacturer of cardiovascular mortality (and heart failure mortality) suggest that treatment with ivabradine (over and above the modifying effect of baseline resting heart rate) is associated with a statistically non-significant (or borderline significant in heart failure) risk reduction. By contrast, beta-blocker therapy of ≥50% of target dose (or any dose for heart failure mortality) is associated with a statistically significant risk reduction. However, the ICERs obtained from the manufacturer's base case model for subgroups of patients based on beta-blockade remained below £11,000 per QALY gained. The ERG notes that the maintenance of benefit for ivabradine (versus standard care alone) is likely to be a result of the reduction in hospitalisation for worsening heart failure; the significance of the effect of ivabradine on the reduction of hospitalisation is maintained across subgroups regardless of beta-blocker dose achieved.

To conclude, the ERG considers that the manufacturer's base case ICER of £8,498 per QALY gained is likely to represent the expected cost effectiveness of adding ivabradine to standard care. However, the ERG notes that the ICER is biased against ivabradine.