NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Ivabradine for treating chronic heart failure

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical Effectiveness

- The manufacturer's submission was based on the subgroup with a baseline resting heart rate of 75 bpm or more, which reflects the licensed population for ivabradine for the treatment of chronic heart failure. The Evidence Review Group (ERG) commented that the evidence in the manufacturer's submission should be interpreted with a level of caution because resting heart rate was not a stratification factor for randomisation in the SHIFT study and because the subgroup was specified after the trial was completed. Does the Committee consider this subgroup to be sufficiently robust given the ERG's concerns?
- What is the Committee's view on the generalisability of the trial to the UK population and practice given that:
  1. The licensed population in the SHIFT study is younger, has a higher proportion of men and more severe heart failure than the typical heart failure population in the UK.
  2. The use of cardiac devices such as cardiac resynchronisation therapy was low ([redacted] of the licensed population).

3. For patients not receiving the target dose of beta-blockers in the licensed population, a high proportion ([redacted]) was due to non-tolerance of beta-blockers resulting from hypotension.
4. Only [redacted] of the licensed population were classified as New York Heart Association (NYHA) class IV heart failure.
5. Ivabradine is contraindicated for unstable heart failure.

- What is the Committee's view on the position of ivabradine in the treatment pathway for chronic heart failure?
- What is the Committee's view on how standard care should be defined for chronic heart failure and how this relates to standard care within the SHIFT study, and whether the outcomes should be presented for each standard care intervention separately?
- The manufacturer's evidence indicated that only 26% of the licensed population was treated with the target dose of beta-blockers at randomisation, and approximately 55% were treated with 50% or more of the target dose. What is the Committee's view on the beta-blocker doses in the trial, particularly whether the SHIFT study participants can be considered to have been treated optimally with beta-blockers?
- What is the Committee's view on the uncertainties identified by the ERG about the benefit of adding ivabradine to optimised standard care when patients are treated with higher levels of beta-blockade?
- The ERG noted that the [redacted] with ivabradine was in the subgroup of patients in NYHA class IV, which was based on only [redacted] patients ([redacted] of the licensed population). Does the Committee consider the evidence on the effectiveness of ivabradine in the subgroup with NYHA class IV heart failure to be limited as stated by the ERG?

Cost-effectiveness

- What is the committee's view on the uncertainty around the benefit of ivabradine on cardiovascular mortality given that the ICER increased to

approximately £40,000 per QALY gained when the risk of cardiovascular mortality was increased using the 95% confidence interval.

Other considerations

- What is the Committee's view on the potential equality issue raised by the patient experts on the higher prevalence of non-revascularisable coronary disease in the Asian population because of the aggressive nature of diabetes as a risk factor?

1 Background: clinical need and practice

1.1 Heart failure is a complex syndrome defined as the inability of the heart to supply sufficient blood flow to meet the body's needs. It is caused by structural or functional abnormalities of the heart, commonly resulting from coronary artery disease. Heart failure can be associated with left ventricular systolic dysfunction (LVSD), which results in a reduced left ventricular ejection fraction (LVEF) if the left pumping chamber's ability to pump is impaired, but it can also be associated with preserved ejection fraction (a minimum ejection fraction of 45%). Symptoms of heart failure are classified by the New York Heart Association (NYHA) system from class I (no limitations) to class IV (inability to carry out any physical activity without discomfort), and commonly include breathlessness, fatigue and ankle swelling. Overall, quality of life in people with heart failure declines as the severity of the disease increases.

1.2 Around 900,000 people in the UK have heart failure and approximately 63,000 people are diagnosed with heart failure each year. Both the prevalence and incidence of heart failure increases with age, with the highest rate occurring in 14% of people aged 85 years and older. The risk of heart failure is higher in men than in

women in all age groups, but there are more women than men with heart failure because of population demographics. Around 30% to 40% of people diagnosed with heart failure die within the first year. In the UK, heart failure accounts for approximately 2% of all NHS inpatient bed-days and 5% of all emergency medical admissions to the hospital.

1.3 The aim of treatment for heart failure is to improve life expectancy, quality of life and to avoid hospital admission. Current strategies include pharmacological management, implantation of devices, surgery and managing comorbid conditions. 'Chronic heart failure: management of chronic heart failure in adults in primary and secondary care' (NICE clinical guideline 108) recommends that all patients be considered for first-line treatment with beta-blockers and an angiotensin-converting enzyme (ACE) inhibitor unless contraindicated or not tolerated.

2 The technology

2.1 Ivabradine (Procoralan, Servier Laboratories) is a heart rate lowering agent which selectively and specifically inhibits the cardiac pacemaker I_f current, which in turn controls the spontaneous diastolic depolarisation in the sinus node that regulates the heart rate. Ivabradine is indicated in chronic heart failure NYHA class II to IV with systolic dysfunction, in patients in sinus rhythm and whose heart rate is 75 bpm or more, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

2.2 The summary of product characteristics lists the following adverse reactions for ivabradine: luminous phenomena (phosphenes), bradycardia, blurred vision, headache, gastrointestinal disorders, uncontrolled blood pressure, atrial fibrillation, eosinophilia,

dyspnoea and muscle cramps. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Ivabradine is administered orally at a recommended starting dose of 5 mg twice daily. This dose maybe increased after 2 weeks of treatment to 7.5 mg twice daily if the resting heart rate is above 60 bpm or decreased to 2.5 mg (half of the 5 mg tablet) twice daily if the resting heart rate is below 50 bpm. Ivabradine is available in 5 mg and 7.5 mg tablets at a net price of £40.17 per 56-tablet pack each (excluding VAT; 'British national formulary' [BNF] edition 63). The manufacturer's submission quoted an average monthly cost of £42.10 (excluding VAT) based on the proportion of patients using 2.5 mg (7%) and 5 mg/7.5 mg (93%) in the SHIFT study. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost-effectiveness of ivabradine within its licensed indication for the treatment of chronic heart failure.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults in sinus rhythm with symptomatic chronic heart failure (NYHA class II to IV) due to left ventricular systolic dysfunction who have been prescribed standard optimal heart failure therapy.	Adults in sinus rhythm with symptomatic chronic heart failure (NYHA class II to IV) due to left-ventricular systolic dysfunction who have been prescribed standard optimal heart failure therapy and have a resting heart rate ≥75 bpm.

The manufacturer's submission focuses on the subgroup of patients with a resting heart rate of 75 bpm or more. This subgroup formed the licensed population based on the recommendation by the Committee for Medicinal Products for Human Use (CHMP) to identify the heart rate threshold at which there is significant

mortality benefit with ivabradine. The Evidence Review Group (ERG) considered the restriction of the population in the manufacturer's submission to the licensed population to be appropriate. They noted that this subgroup of patients was younger and had more severe heart failure than would typically be seen in clinical practice in the UK. However, it agreed with the manufacturer that the population analysed was similar to the populations included in other key heart failure trials.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Ivabradine	
Comparators	Standard treatment without ivabradine	
Outcomes	• Cardiovascular mortality • All-cause mortality • Hospitalisation due to heart failure • All-cause hospitalisation • Adverse effects of treatment • Health-related quality of life	
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective.	

3.2 Ivabradine is proposed as an add-on therapy for the treatment of heart failure due to left ventricular systolic dysfunction in the following circumstances:

- Patients in sinus rhythm receiving standard care, for whom beta-blockers are contraindicated or who are intolerant to them, who have a resting heart rate of 75 bpm or more.

- Patients in sinus rhythm receiving standard care including beta-blockers at maximally tolerated doses whose resting heart rate remains at 75 bpm or more.

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted a systematic literature search and identified only 1 randomised controlled trial that assessed the effect of ivabradine in people with heart failure, the SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) study. SHIFT was an international, multicentre, randomised, double-blind, placebo-controlled trial comparing ivabradine with placebo for the treatment of moderate to severe heart failure and left ventricular systolic dysfunction. The study was undertaken in 625 centres in 37 countries and lasted from 12 to 36 months in the active double-blind treatment period with an extension to 52 months. The clinical effectiveness evidence presented in the manufacturer's submission was based on this trial alone although details were also provided for the SHIFT patient-reported outcomes (SHIFT-PRO) sub-study. This sub-study was of a representative sample of the main trial population and was undertaken to evaluate the effects of ivabradine compared with placebo on health-related quality of life in patients with heart failure and LVSD.

4.2 Patients with symptomatic heart failure with an LVEF of 35% or lower and in sinus rhythm with a heart rate of 70 bpm or more receiving stable background treatment for heart failure were considered eligible for participation in the SHIFT study. After screening, 6505 patients were randomised to receive either ivabradine or placebo in addition to ongoing optimal therapy for heart failure (as assessed by the investigator responsible for the patient). All patients received 5 mg of ivabradine or matching

placebo twice daily at day 0. Then the dose was either maintained, up-titrated to 7.5 mg twice daily or down-titrated to 2.5 mg twice daily depending on resting heart rate and tolerability. All analyses were based on intention to treat even though a total of 1190 patients died, withdrew consent or were lost to follow-up.

4.3 The allocation groups in the SHIFT trial were well balanced with no relevant between-group differences in the baseline characteristics of the patients reported. The mean age was 60.4 years, 76% of the participants were male and most were white (89%). Mean heart rate was 79.9 bpm and mean LVEF was 29%. Heart failure was of ischaemic cause in 68% of the patients and patients were equally distributed between NYHA class II, III or IV. Alcohol consumption and smoking status were also similar between the trial arms with less than 20% of the participants being current smokers in both arms. The background therapies were also similar in both arms (ACE inhibitors/angiotensin receptor blockers: 91%, diuretics: 84%, beta-blocker: 89%, aldosterone antagonists: 61% and cardiac devices (implantable cardioverter defibrillator: 3% and cardiac resynchronisation therapy: 1%).

4.4 Subgroups were predefined in terms of age, sex, beta-blocker intake at randomisation, primary cause of heart failure, NYHA class, presence of diabetes, presence of hypertension and heart rate above and below the median of 77 bpm. Another subgroup based on a baseline heart rate of 75 bpm or more (n=4150) was identified post hoc and this was used to inform the licensed population. The manufacturer stated in its submission that this subgroup was identified after the CHMP recommended identifying the heart rate threshold at which there is significant mortality benefit. The manufacturer's economic model was also based on

this post-hoc subgroup. Other post-hoc subgroups identified were based on age (75 years or older and 70 years or older).

4.5 The baseline characteristics of the subgroup with a baseline heart rate of 75 bpm or more (the licensed population) were similar to the main trial population. The mean age for this subgroup was 59.6 years and, like the main trial population, they were mostly male (77%) and white [redacted]. There were no relevant baseline differences between the treatment groups in this population including mean heart rate (84.5) and distribution of NYHA class. The background therapies received were also similar to the main trial population (ACE inhibitors/angiotensin receptor blockers: 90%, diuretics: 84%, beta-blocker: 87%, aldosterone antagonists: 61.6% and cardiac devices (implantable cardioverter defibrillator: [redacted] and cardiac resynchronisation therapy: [redacted]).

Table 1 Baseline demographic characteristics, history of heart failure and other medical history at baseline (main trial population and licensed population subgroup)

	Heart rate ≥70 bpm at baseline (n=6505)		Heart rate ≥75 bpm at baseline (n=4,150)	
	Ivabradine n=3241	**Placebo n=3264**	**Ivabradine n=2052**	**Placebo n=2098**
Age (years)				
Mean ± SD	60.7 ± 11.2	60.1 ± 11.5	59.7 ± 11.23	59.5 ± 11.71
Median (range)	61 (19; 89)	60 (19; 92)	60 (52; 68)	60 (52; 68)
Sex n (%)				
Male	2462 (76.0)	2508 (76.8)	1570 (76.5)	1617 (77.1)
Ethnic origins n (%)				
White	2879 (88.8)	2892 (88.6)	[redacted]	[redacted]
Asian	268 (8.3)	264 (8.1)		
Black	32 (1.0)	43 (1.3)		
Other	62 (1.9)	65 (2.0)		
Height (cm)				
n	3240	3264	[redacted]	[redacted]
Mean ± SD	169.6 ± 8.8	169.6 ± 8.8		
Median (range)	170 (135; 197)	170 (109; 198)		
Weight (kg)				
Mean ± SD	80.9 ± 17.2	80.7 ± 17.1	[redacted]	[redacted]
Median (range)	80 (27; 159)	79 (29; 170)		
Body mass index (kg/m^2)				
n	3240	3264	2052	2098
Mean ± SD	28.0 ± 5.1	28.0 ± 5.0	28.1 ± 5.3	27.9 ± 5.1
Median (range)	27.4 (13.7; 51.6)	27.3 (15.1; 59.5)	27.4 (24.4; 31.2)	27.2 (24.4; 30.7)
Heart rate (bpm)				
n	3240	3261	2052	2098
Mean ± SD	79.7 ± 9.5	80.1 ± 9.8	84.3±9.1	84.6±9.4
Median (range)	77 (48; 130)	77 (58; 142)	–	–
Sitting SBP (mmHg)				
Mean ± SD	122.0 ± 16.1	121.4 ± 15.9	121.6	121.2
Median (range)	120 (76; 179)	120 (78; 180)	–	–
Sitting DBP (mmHg)				
Mean ± SD	75.7 ± 9.6	75.6 ± 9.4	75.8	75.7
Median (range)	77 (42; 110)	76 (40; 120)	–	–
eGFR (creatinine clearance) (ml/min/1.73m^2)				
n	3233	3252	[redacted]	[redacted]
Mean ± SD	74.6 ± 22.9	74.8 ± 23.1	75.7 ± 23.5	75.5 ± 23.1
Median (range)	73 (23; 263)	73 (17; 331)		
Smoking habits n (%)				
Yes	541 (16.7)	577 (17.7)	381 (18.6)	402 (19.2)
Previous	1355 (41.8)	1364 (41.8)	410 (20.0)	857 (40.9)
Never	1345 (41.5)	1323 (40.5)	1039 (50.6)	839 (40.0)
Alcohol consumption n (%)				
Yes	988 (30.5)	940 (28.8)	[redacted]	[redacted]
Previous	628 (19.4)	648 (19.9)		
Never	1625 (50.1)	1676 (51.4)		
Chronic heart failure				

Duration since HF diagnosis (years); mean ± SD		3.5 ± 4.2	3.5 ± 4.2	3.5 ± 4.1	3.4 ± 4.0
Primary cause of HF n (%)					
Ischaemic		2215 (68.3)	2203 (67.5)	1359 (66.2)	1363 (65.0)
Non-ischaemic		1026 (31.7)	1061 (32.5)	693 (33.8)	735 (35.0)
Documented hospital admission for worsening HF in previous 12 months, n (%)	Yes	42 (1.3)	37 (1.1)	[redacted]	[redacted]
	No	3199 (98.7)	3227 (98.9)		
NYHA class					
Class II, n (%)		1585 (48.9)	1584 (48.5)	977 (47.6)	975 (46.5)
Class III, n (%)		1605 (49.5)	1618 (49.6)	1035 (50.4)	1076 (51.3)
Class IV, n (%)		50 (1.5)	61 (1.9)	40 (1.6)	47 (2.2)
LVEF (%)					
Mean ± SD		29.0 ± 5.1	29.0 ± 5.2	28.7 ± 5.18	28.54 ± 5.27
Median (range)		30.0 (9; 39)	30.0 (7; 37)	30.0 (9; 39)	30.0 (7; 36)
Other medical histories, n (%)					
Coronary artery disease		2361 (72.9)	2371 (72.6)	[redacted]	[redacted]
Hypertension		2162 (66.7)	2152 (65.9)	1333 (65.0)	1349 (64.3)
Myocardial infarction		1829 (56.4)	1837 (56.3)	1124 (54.8)	1138 (54.2)
Diabetes		973 (30.0)	1006 (30.8)	638 (31.1)	665 (31.7)
Atrial fibrillation and/or flutter		263 (8.1)	259 (7.9)	154 (7.5)	162 (7.7)
Stroke		228 (7.0)	295 (9.0)	141 (6.9)	189 (9.0)
Renal failure		218 (6.7)	202 (6.2)	122 (6.0)	121 (5.8)

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; SBP, systolic blood pressure; SD, standard deviation

Source: manufacturer's submission (table 6)

4.6 The primary outcome in the SHIFT main trial was a composite endpoint of first event of cardiovascular death or hospital admission for worsening heart failure. This was carried out using a survival analysis based on a time-to-first event estimated with the Kaplan-Meier method. Secondary outcomes included mortality and hospital admission endpoints, as well as change in heart rate, change in NYHA class, change in global assessment of heart failure symptoms and efficacy in patients aged 70 years or older (post-hoc analysis in the main trial population).

4.7 In the SHIFT-PRO sub-study (n=5038), health-related quality of life was estimated using the EuroQol 5 Dimensions (EQ5D) questionnaire and Kansas City Cardiomyopathy Questionnaire

(KCCQ). Analysis in this sub-study was also performed according to the same predefined subgroups specified in the main trial population, with the exception of presence of diabetes and hypertension. An additional subgroup was specified according to whether or not they had received at least half the target dose of beta-blockers at randomisation. The manufacturer's submission noted that they were no relevant differences in baseline demographics and disease characteristics between the main trial population and the licenced population and also in the SHIFT-PRO sub-study.

Main SHIFT trial population

4.8 In the main trial population, the primary outcome of first event of cardiovascular death or hospital admission for worsening heart failure was shown using a Cox proportional hazards model adjusted for beta-blocker intake at randomisation, with a hazard ratio (HR) estimate of 0.82 (95% confidence interval [CI] 0.75 to 0.90, p<0.0001), representing a significant relative risk reduction of 18% with ivabradine. This composite endpoint was driven more by the rate of hospital admission for worsening heart failure (HR 0.74, 95% CI 0.66 to 0.83) than by the rate of cardiovascular death (HR 0.91, 95% CI 0.80 to 1.03) because people are often admitted to hospital before they die. An unadjusted Cox proportional hazards model confirmed the results of the main analysis with the same HR, CI and p value. Prognostic factors analysis based on a Cox proportional hazards model adjusted for beta-blocker intake, NYHA class, LVEF, aetiology of heart failure, age systolic blood pressure, heart rate and estimated glomerular filtration rate also showed a significant benefit with ivabradine (HR 0.83, 95% CI 0.75 to 0.91, p<0.0001).

4.9 The superiority of ivabradine over placebo was shown to be consistent across the predefined subgroups in the main trial population. The interaction tests all had p values greater than 0.05, except the subgroups based on baseline heart rate (less than the 77 bpm [the median heart rate] or 77 bpm or more]) with p=0.0288, indicating a greater effect of ivabradine in patients with a higher heart rate at baseline (HR 0.75, 95% CI 0.67 to 0.85), although ivabradine was favoured more on both sides of the median. The hazard ratio for the primary composite endpoint for people receiving at least 50% of the target dose of beta-blocker showed a trend towards benefit in the ivabradine group although this did not reach statistical significance (HR 0.90, 95% CI 0.77 to 1.04). The prognostic factors analysis produced similar results (HR 0.92, 95% CI 0.79 to 1.07).

4.10 For the mortality outcomes, death from heart failure was reduced significantly by 26% (HR 0.74, 95% CI 0.58 to 0.94, p=0.014) in the ivabradine group compared with the placebo group, while non-significant reductions favouring ivabradine were seen for all-cause death (HR 0.91, 95% CI 0.80 to 1.02, p=0.092) and cardiovascular death (HR 0.91, 95% CI 0.80 to 1.03, p=0.128). The greatest reduction in hospital admission was for worsening heart failure (HR 0.74, 95% CI 0.66 to 0.83, p<0.0001). Rates of hospital admission because of cardiovascular problems (HR 0.85, 95% CI 0.78 to 0.92, p=0.0002) and all-cause hospital admission (HR 0.89, 95% CI 0.82 to 0.96, p=0.0027) were also statistically significantly lower. Results were similar for unplanned admission because of cardiovascular problems and all-cause admission.

4.11 For other secondary outcomes, heart rate decreased by 15.4 bpm in the ivabradine group and 4.6 bpm in the placebo group at day 28 for the main trial population. The effect of ivabradine was

maintained because the mean reduction in heart rate at last visit was 12 bpm and 4.1 bpm for the ivabradine and placebo group. There was a statistically significant improvement in NYHA class in the main trial population (27.6% in the ivabradine group and 24% in the placebo group, p=0.0010). There were also statistically significant improvements with ivabradine compared with placebo in patient-reported assessment (71.8% and 67.6% respectively, p=0.0005) and physician-reported assessment (61.1% and 57.0% respectively, p=0.0011) of heart failure symptoms. Analysis based on the subgroup of patients aged 70 years or older showed that the incidences of primary composite endpoint and main secondary outcomes were higher in this subgroup than in the main trial population.

4.12 Further analysis was carried out by the manufacturer to assess the impact of baseline beta-blocker dose on the efficacy of ivabradine in the main SHIFT population. For the primary composite endpoint, the relative effects for the 5 categories of beta-blocker intake were: HR 0.71, 95% CI 0.55 to 0.93, p=0.012 (no beta-blocker), HR 0.74, 95% CI 0.59 to 0.92, p=0.007 (less than 25% of target dose), HR 0.81, 95% CI 0.68 to 0.98, p=0.029 (more than 25% but less than 50% of target dose), HR 0.88, 95% CI 0.72 to 1.07, p=0.193 (more than 50% but less than 100% of target dose) and HR 0.99, 95% CI 0.79 to 1.24, p=0.913 (100% or more of target dose). There were similar trends in efficacy across the beta-blocker categories for the component outcomes of hospital admission for worsening heart failure and cardiovascular death. The manufacturer noted that this could be a result of lower doses of beta-blockers being associated with higher heart rate because beta-blockers primarily reduce heart rate. There were no statistically significant differences across the beta-blocker categories. These findings suggest that the efficacy of ivabradine is primarily driven by heart rate and not by

beta-blocker dose. After clarification, the manufacturer provided the absolute numbers for the primary composite outcome and key secondary outcomes for the subgroups of the licensed population according to their beta-blocker category (details of the analysis are in section 4.24).

Licensed Population

4.13 In the subgroup with a baseline heart rate of 75 bpm or more (the threshold at which there was a significant mortality benefit, identified at the request of the CHMP to inform the licensed population), the incidence of the primary composite endpoint was statistically significantly lower in the ivabradine group than the placebo group (26.6% and 32.8% respectively, p<0.0001). The hazard ratio showed a clinically and statistically significant reduction of 24% in the risk of the composite endpoints (HR 0.76, 95% CI 0.68 to 0.85). This was in line with the predefined subgroup analysis on median heart rate which revealed that baseline heart rate modified the treatment effect of ivabradine.

4.14 There was a significant improvement in all secondary outcomes for the licensed population compared with the main SHIFT population. There were significant reductions in all mortality outcomes: cardiovascular death (HR 0.83, 95% CI 0.71 to 0.97, p=0.0166), heart failure death (HR 0.61, 95% CI 0.46 to 0.81, p=0.0006) and all-cause death (HR 0.83, 95% CI 0.72 to 0.96, p=0.0109). Results similarly favoured ivabradine for hospital admission for cardiovascular problems (HR 0.79, 95% CI 0.71 to 0.88, p<0.0001), for worsening heart failure (HR 0.70, 95% CI 0.61 to 0.80, p<0.0001) and for all causes (HR 0.82 95% CI 0.75 to 0.90, p<0.0001).

4.15 In the licensed population, heart rate decreased by 17.4 bpm and 5.7 bpm at day 28, and 14.5 bpm and 5.8 bpm at last visit for the ivabradine and placebo groups respectively. The manufacturer noted that the higher drop in the licensed population was consistent with a higher mean baseline heart rate of 84 bpm in this subgroup compared with 80 bpm in the main trial population. This was confirmed to be in line with previous ivabradine trials, which show that greater reductions in heart rate are associated with higher resting heart rate. There was a statistically significant improvement in NYHA class in this subgroup [redacted] in the ivabradine group and [redacted] in the placebo group. There were also [redacted] improvements with ivabradine in patient-reported [redacted] compared with [redacted] and physician-reported assessment [redacted] compared with [redacted] of heart failure symptoms as with the main trial (p values not provided in the manufacturer's submission).

4.16 In the PRO-SHIFT sub-study, which was based on the main SHIFT population, quality of life was estimated using the generic EQ-5D index score and EQ-5D visual analogue scale (VAS) health measures. Three forms of analyses were performed based on using '0' as the last post-baseline value for deceased patients (main analysis), using the last post-baseline value for deceased patients (analysis of surviving patients) and change from baseline to month 12 in the main analysis. For the EQ-5D index score measure, quality of life worsened from baseline to the last assessment in the ivabradine group [redacted] and placebo group [redacted] in the main analysis. However, there was an improvement in quality of life from baseline to the last assessment for the analysis of surviving patients in the 2 treatment groups with a [redacted] in favour of ivabradine. Quality of life also improved from baseline to month 12 in both groups but there were

[redacted]. The manufacturer suggested that this was because of the minimal impact of death in the 12-month analysis because there were fewer deaths than in the whole study. There were similar results with the EQ-5D VAS measure.

Table 2 EQ-5D index score and VAS health measures

	Ivabradine	Placebo	Difference in change in score: ivabradine – placebo (± SE) 95% CI; p value
Change from baseline to last assessment			
EQ-5D index score (mean ± SD) Including scoring death as 0: Baseline Final Δ Analysis of surviving patients: Baseline Final Δ	n=1925	n=1926	
Change from baseline to month 12			
EQ-5D index score (mean ± SD) Including scoring death as 0: Baseline Final Δ	n=1770	n=1789	
Change from baseline to last assessment			
EQ-VAS (mean ± SD) Including scoring death as 0: Baseline Final Δ Analysis of surviving patients: Baseline Final Δ	n=2018	n=2018	
Change from baseline to month 12			
EQ-VAS (mean ± SD) Including scoring death as 0: Baseline Final Δ	n=1769	n=1791	
CI, confidence interval; SD, standard deviation; SE, standard error			

Source: manufacturer's submission (table 20 and 22)

4.17 A mixed regression model was used to estimate quality of life using EQ-5D index scores with UK population tariff values. This showed that quality of life was significantly improved by [redacted] in the ivabradine group for the licensed population. The KCCQ disease-specific measure was also used and it showed [redacted]

differences of [redacted], [redacted] and 2.6 (95% CI 0.7 to 4.5, p=0.008) for the main analysis, analysis of surviving patients and change from baseline to 12-month analysis respectively [redacted].

4.18 The safety set (n=6492 main trial cohort; n=4141 licensed population) was described by the manufacturer as the patients who received at least 1 dose of any study treatment. The adverse events that occurred on treatment (between the first study drug intake and last intake plus 2 days) were analysed in this safety population. The following adverse events occurred more frequently with ivabradine than with placebo in the licensed population: symptomatic bradycardia (4.1% and 0.7% respectively), atrial fibrillation (7.9% and 6.8% respectively) and phosphenes (2.8% and 0.5% respectively). There were similar results for the main trial population (see table 3). However, other serious adverse events and fatal events were higher in the placebo group in the 2 populations. The manufacturer noted that the tolerability of ivabradine was not limited by baseline heart rate because there were no differences in the adverse events leading to withdrawal between the main trial population and the licensed population.

Table 3 Summary of adverse events 'on treatment': main trial population (70 bpm or more) and licensed population (75 bpm or more)

	Heart rate at baseline 70 bpm or more			Heart rate at baseline 75 bpm or more		
	Ivabradine (n=3232)	**Placebo n=3260)**	**Relative risk (95% CI)**	**Ivabradine (n=2046)**	**Placebo n=2095)**	**Relative risk (95% CI)**
All emergent adverse events	2414 (74.7%)	2392 (73.4%)	1.02 (0.99, 1.05)	1554 (76.0%)	1607 (76.7%)	0.99 (0.96, 1.02)
All serious emergent adverse events	1369 (42.4%)	1481 (45.4%)	0.93 (0.88, 0.99)	892 (43.6%)	1020 (48.7%)	0.90 (0.84, 0.96)
All emergent adverse events leading to drug withdrawal	467 (14.4%)	416 (12.8%)	1.13 (1.00, 1.28)	300 (14.7%)	295 (14.1%)	1.04 (0.90, 1.21)
Selected emergent adverse events						
Cardiac failure	701 (21.7%)	846 (26.0%)	0.84 (0.77, 0.91)	487 (23.8%)	609 (29.1%)	0.82 (0.74, 0.91)
Symptomatic bradycardia	148 (4.6%)	28 (0.9%)	5.33 (3.57, 7.96)	84 (4.1%)	14 (0.7%)	6.14 (3.50, 10.78)
Asymptomatic bradycardia	181 (5.6%)	45 (1.4%)	4.06 (2.94, 5.60)	98 (4.8%)	25 (1.2%)	4.01 (2.60, 6.20)
Atrial fibrillation	267 (8.3%)	217 (6.7%)	1.24 (1.04, 1.47)	161 (7.9%)	143 (6.8%)	1.15 (0.93, 1.43)
Phosphenes	89 (2.8%)	16 (0.5%)	5.61 (3.30, 9.53)	57 (2.8%)	11 (0.5%)	5.31 (2.79, 10.09)
Blurred vision	17 (0.5%)	7 (0.2%)	2.45 (1.02, 5.90)	11 (0.5%)	7 (0.3%)	1.61 (0.62, 4.14)

Source: manufacturer's submission (table 24)

Evidence Review Group comments

4.19 The ERG stated that the literature search conducted by the manufacturer was appropriate, all relevant studies had been identified, and that the SHIFT trial on which the manufacturer's submission was based was relevant to the decision problem in its analysis. The ERG was satisfied that SHIFT was a well-designed

randomised controlled trial with a robust method of randomisation. However they highlighted that only 12 patients (0.2%) in the study were recruited from the UK, but it noted the manufacturer's comment about the difficulties in gaining study approval within the UK. The ERG also stated that the low UK participant numbers may have resulted from the difficulty in identifying eligible patients if patients were attending heart failure centres and had good titration of beta-blocker therapy. It also noted that the licensed population was younger and had a higher proportion of men and more severe heart failure than a typical UK heart failure patient population, but it recognised that the baseline characteristics of the licensed population were similar to other key heart failure studies. However, the ERG considered that the results of the SHIFT trial were robust and generalisable to a UK population because there was evidence to suggest that the patients in the trial received standard treatments at optimal doses.

4.20 The ERG noted that the clinical effectiveness evidence of ivabradine was based on a post-hoc subgroup of patients with a resting heart rate of 75 bpm or more without prior stratification based on resting heart rate, but in line with ivabradine's licence. Therefore it considered that the evidence presented should be interpreted with a level of caution because there is likely to be an imbalance between the groups in terms of heart rate and potential unknown confounders. However, the ERG acknowledged that the baseline characteristics were well balanced between the treatment groups in the main trial population and the licensed population.

4.21 The ERG was aware that only approximately 26% of the main trial population and the licensed population were each treated with the recommended target dose of beta-blocker, and 55.4% of the licensed population were treated with 50% or more of the

recommended dose despite the recommendations in the SHIFT protocol. It was concerned that the patients who were not treated with the target dose of beta-blocker may not have been optimally treated. The ERG considered the manufacturer's comment that the proportion of patients treated with the target dose of beta-blockade in the SHIFT trial was greater than in UK clinical practice, but noted that it was considerably smaller than those in other key heart failure trials evaluating beta-blockers. However, the ERG highlighted that beta-blocker doses were generally maintained in 2 of the previous trials, even though the manufacturer had previously stated that patients could often not be maintained on the doses after titration because of treatment intolerance. The ERG also noted the low use of devices in the SHIFT trial and considered that this could have resulted from the exclusion of patients with pacemakers from the trial.

4.22 The ERG noted that the greatest benefit of ivabradine was the reduction in heart failure deaths (HR 0.61; 95% CI 0.46 to 0.81, p=0.0006), which supports the observation that the results were generally driven by the cause-specific endpoints of hospital admission for heart failure and heart failure deaths in both populations. The ERG noted that a [redacted] proportion of patients in the ivabradine group of the licensed population improved by 1 NYHA class or more at their last visit from their baseline classification compared with the placebo group [redacted]. However, they noted that there was [redacted] between groups in the proportion of patients with worsening NYHA classification [redacted]

4.23 The ERG noted that treatment-related adverse events occurred more frequently in the ivabradine group (17.8%) than the placebo group (8.3%) in the main trial population. It felt that this was likely to

be the same for the licensed population because the most common adverse events were the same as in the main trial population. The ERG highlighted that the reported adverse events (apart from inadequate blood pressure control) were similar to those reported in the BEAUTIFUL trial (10,917 randomised patients) which assessed the effects of ivabradine plus standard care in patients with coronary artery disease and LVSD.

4.24 The ERG undertook exploratory analysis of the data provided by the manufacturer on the primary and secondary outcomes of the licensed population according to their beta-blocker dosage at randomisation. This exploratory analysis suggested a trend in the [redacted] of ivabradine compared with placebo with increasing beta-blockade for the primary composite outcome: [redacted] (no beta-blocker), [redacted] (less than 25% of target dose), [redacted] (more than 25% but less than 50% of target dose), [redacted] (more than 50% but less than 100% of target dose) and [redacted] (100% or more of target dose). A [redacted] of ivabradine was observed in the secondary outcomes of cardiovascular death ([redacted] [no beta-blocker], [redacted] [less than 25% of target dose], [redacted] [more than 25% but less than 50% of target dose], [redacted] [more than 50% but less than 100% of target dose] and [redacted] [100% or more of target dose]) and all-cause death ([redacted] [no beta-blocker], [redacted] [less than 25% of target dose], [redacted] [more than 25% but less than 50% of target dose], [redacted] [more than 50% but less than 100% of target dose] and [redacted] [100% or more of target dose]). However, the ERG noted that ivabradine was associated with a [redacted] in the heart failure-

specific outcomes irrespective of the category of beta-blocker dose, although some of the differences between groups [redacted]; heart failure death ([redacted] [no beta-blocker], [redacted] [less than 25% of target dose], [redacted] [more than 25% but less than 50% of target dose], [redacted] [more than 50% but less than 100% of target dose] and [redacted] [100% or more of target dose]) and hospital admission for worsening heart failure ([redacted] [no beta-blocker], [redacted] [less than 25% of target dose], [redacted] [more than 25% but less than 50% of target dose], [redacted] [more than 50% but less than 100% of target dose] and [redacted] [100% or more of target dose]), The ERG highlighted that at target beta-blocker dose, ivabradine was associated with [redacted] for the cardiovascular mortality outcome, and the direction of effect [redacted].

4.25 The ERG further grouped the patients into 'no beta-blocker' or 'low dose (less than 25% of target dose)', and 'moderate/high dose (25% or more of target dose, including target dose)'. Ivabradine was associated with [redacted] in all outcomes compared with placebo in the none/low-dose group except for non-heart failure cardiovascular death, which was [redacted]. In the moderate/high-dose group, with the exception of the primary composite outcome and hospital admission because of heart failure, most differences between groups [redacted]. The ERG considered the manufacturer's comment that variation in the clinical effect of ivabradine is linked with baseline resting heart rate and not baseline level of beta-blockade, but noted that baseline mean

resting heart rates were [redacted] across the 5 beta-blocker categories in the licensed population. It also noted that there was no [redacted] in all-cause mortality despite a [redacted] in heart rate of approximately [redacted] with ivabradine compared with placebo across the beta-blocker categories. Therefore, the ERG considered that the variations in clinical effect in the ERG's exploratory analysis could be associated with the level of beta-blockade received. The ERG considered that their exploratory analyses suggests that 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 higher levels of beta-blockade. However, they emphasised that these analyses are speculative and based on subgroups of subgroups and should be interpreted with caution.

4.26 The ERG also undertook exploratory analysis of the data provided by the manufacturer on patients aged 70 years or older in the licensed population, and found that ivabradine was associated with a [redacted] for all outcomes assessed. Ivabradine [redacted] the risk of the incidence of primary composite outcome by [redacted] compared with placebo. The [redacted] was in the [redacted] of cause-specific outcome of death from heart failure [redacted] The ERG highlighted that these analyses are speculative and should be interpreted with caution because they are based on subgroups of subgroups.

4.27 The ERG also found that ivabradine was associated with [redacted] in the primary and secondary outcomes across all NYHA class subgroups in the licensed population: primary composite outcome (NYHA II – [redacted], NYHA III –

[redacted], NYHA IV –[redacted], cardiovascular death (NYHA II –[redacted], NYHA III –[redacted]NYHA IV –[redacted], all-cause death (NYHA II –[redacted], NYHA III –[redacted], NYHA IV –[redacted], heart failure death (NYHA II –[redacted], NYHA III –[redacted], NYHA IV –[redacted], and hospital admission for worsening heart failure (NYHA II –[redacted], NYHA III –[redacted], NYHA IV –[redacted]. It noted that the [redacted] was in NYHA class IV which was based on only [redacted] patients, creating an uncertainty in the effectiveness of ivabradine in this subgroup. The ERG considered that the exploratory subgroup analyses suggest that ivabradine effect is [redacted] of age and severity of heart failure based on NYHA class.

5 Comments from other consultees

5.1 Professional groups and clinical specialists stated that chronic heart failure is currently treated in line with the guidance on chronic heart failure (NICE clinical guideline 108), which recommends using ACE inhibitors or beta-blockers first line unless contraindicated or not tolerated. The professional groups and clinical specialists acknowledged that ivabradine is the only alternative heart rate lowering drug for people with LVSD and in sinus rhythm for whom beta-blockers are not suitable. However, they stressed that there is a potential risk that optimal use of beta-blockers will be limited if ivabradine is adopted too early – as has been seen with some practitioners – as well as cost to the NHS and likely mortality cost to patients. They noted that ivabradine is

currently being used within its licensed indication for the symptomatic relief of stable angina and for managing heart failure in a few heart failure services in UK practice.

5.2 Professional groups and clinical specialists considered that ivabradine should ideally be used in specialist clinics based in secondary care so that patients can be properly monitored, especially during initiation and titration of doses. However, a clinical specialist noted that experienced GPs with special interests and heart failure nurses may also be able to initiate and titrate ivabradine in some primary care settings. The professional groups and clinical specialists emphasised the need for strict criteria to ensure that ACE inhibitors and beta-blockers are used optimally first line before considering ivabradine and to ensure appropriate selection of patients, particularly for those with complex comorbidities, the elderly and those showing intolerance to beta-blockers. Clinical specialists indicated that patients with low blood pressures in whom it may be difficult to rapidly up-titrate beta-blockers may also derive particular benefits from ivabradine. However they noted that ivabradine is contraindicated in people with severe hypotension (less than 90/50).

5.3 Professional groups and clinical specialists noted that the SHIFT trial is the only study that currently supports the use of ivabradine for chronic heart failure. The clinical specialists considered that the results from the trial would extrapolate well to a UK setting even though SHIFT patients were slightly younger than in clinical practice. They also stated that the primary SHIFT outcomes (mortality and hospital admission) and quality of life were important outcomes for people with heart failure. However the clinical specialists noted that only 11 patients from the UK were included in the SHIFT study and they expressed their concern that ivabradine

may be useful only for a few patients who genuinely cannot tolerate more than low doses of beta-blockers. The clinical specialists stated that ivabradine appears to be much simpler and safer to use compared with most drugs for heart failure although there are recognised side effects such as bradycardia, atrial fibrillation and phosphenes. They stressed the need for additional clinical trial data to better understand the place of ivabradine in the treatment of heart failure.

5.4 Patient experts stated that ivabradine will provide relief for people with ischaemic cardiomyopathy, particularly those with non-revascularisable coronary disease, which appears to be more prevalent in the Asian population because of the aggressive nature of diabetes as a risk factor. They noted that the only disadvantage of ivabradine may be related to the cost for individual patients and also indicated that its use may be limited if beta-blockers are used effectively already. The patient experts also stated that people unable to take beta-blockers are likely to benefit more from treatment with ivabradine.

5.5 The patient experts acknowledged that studies on ivabradine for chronic heart failure were limited and they said that there is an ongoing debate about the optimal use of baseline medical therapy, particularly beta-blockade in the trial. They stated that ivabradine might provide symptomatic and prognostic benefit in a small number of heart failure patients and recommended that all patients be treated similarly irrespective of ethnicity.

5.6 NHS organisations stated that standard practice involves using beta-blockers as first-line agents to treat because evidence shows they reduce morbidity and mortality. They indicated that ivabradine is used as an alternative if beta-blockers cannot be used, although

current use is low locally, making it difficult to determine its impact on resources. NHS organisations said they believe that beta-blockers would remain in use for most patients after the introduction of ivabradine because ivabradine would be used for patients currently not being treated because they cannot tolerate beta-blockers or because beta-blockers are contraindicated. They also noted that ivabradine is currently only started by consultants or GPs with a special interest and the NHS organisations thought that use could be generalised because there are no requirements for monitoring. The NHS organisations thought that ivabradine would cost an additional £38,500 per year approximately, based on modelling formula. They noted that having more heart failure nurses for titration may avoid secondary care referrals and reduce hospital admissions, and they said that any additional training would be the same as with any new therapies.

6 Cost-effectiveness evidence

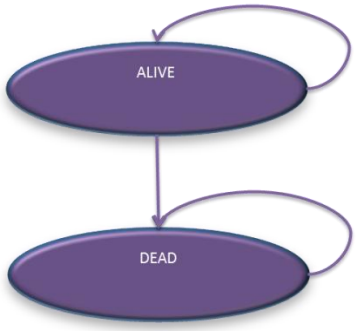
6.1 In a systematic review of the literature the manufacturer did not identify any study on the cost effectiveness of ivabradine for treating chronic heart failure.

6.2 The economic evaluation was based on the post-hoc subgroup of patients from the SHIFT study with a baseline heart rate of 75 bpm or more. The manufacturer stated that this subgroup reflected the licence for ivabradine, that is people with chronic heart failure NYHA class II to IV with systolic dysfunction, in sinus rhythm and whose heart rate is 75 bpm or more, who are being treated with ivabradine in combination with standard therapy including beta-blockers, or for whom beta-blockers are contraindicated or not tolerated. The regression equations for mortality, NYHA class distribution, hospital admission and quality of life used in the

analysis were based on data from the entire SHIFT cohort rather than developing risk equations based solely on the licensed population. This was to avoid breaking randomisation and reducing the predictive power of the risk equations because of smaller sample size. However, the risk equations were adjusted for patient baseline heart rate to predict estimates for the licensed population with a heart rate of 75 bpm or more.

6.3 The manufacturer developed a Markov cohort model consisting of 2 states (alive and dead). The difference in quality of life of patients has been captured according to NYHA class in the 'alive' state of the model without modelling the NYHA classes as separate health states. The model has a lifetime time horizon consisting of monthly cycles, includes a half-cycle correction, and both costs and benefits were discounted at 3.5%. The analysis was performed from the perspective of the NHS and personal social services. Standard care was modelled according to SHIFT trial patterns because the use of heart failure medications in the trial was higher than current treatment patterns in the UK.

Figure 1 Model structure



Source: manufacturer's submission (section 6.2.2)

6.4 The manufacturer estimated the risk of non-cardiovascular death based on age and sex-adjusted UK national life table data from the Office for National Statistics rather than SHIFT data because it provides a larger, UK-specific data source. This was assumed to be the same across treatment groups and no treatment effect was modelled for this endpoint. The risk of cardiovascular mortality (both heart failure and other non-heart failure cardiovascular death) for the within-trial period was estimated using the Gompertz parametric survival regression model based on the full SHIFT cohort in the base-case analysis. The survival models based on the exponential and Weibull parametric distributions as well as Kaplan Meier data were included as part of the sensitivity analyses. The cardiovascular mortality risk equation was estimated adjusting for a series of baseline patient characteristics (including age, sex, NYHA class, heart failure duration, body mass index, medical history, baseline use of heart failure medications) to generate different estimates of mortality. The Gompertz distribution was also used to extrapolate cardiovascular mortality beyond the trial period although only approximately 17% of the standard care arm of SHIFT died at the end of the study. As a result of the uncertainty generated by using a small proportion to extrapolate mortality for the rest of the cohort, the manufacturer considered mortality data from an external data source (CARE-HF data; Cleland, 2010) in sensitivity analyses. The extrapolation assumes that 50% of the cohort would have died after 2000 days (65 months).

6.5 The distribution of patients in each NYHA class over time was estimated from a generalised ordered regression (a proportional odds model) developed from SHIFT data. It predicted the distribution of NYHA class adjusting for treatment and time covariates but not patient baseline characteristics. By the third year the proportion of patients in class III and IV reduced from 40.2% to

36.9% in the ivabradine arm and from 44% to 40.6% in the standard care arm while those in class II increased from 58.4% to 61.4% and from 54.9% to 58.1% in the ivabradine arm and standard care arm respectively. Because of the lack of external evidence to predict the distribution of patients by NYHA class beyond the trial period, the model assumed that the proportions remained fixed after the trial based on the last observation in the trial at 29 months (although the absolute numbers in each category are expected to vary according to the number of patients alive).

6.6 The rate of heart failure, cardiovascular and all-cause hospital admission per person month was estimated using the Poisson regression model based on the entire SHIFT cohort and converted into a monthly transition probability in the economic model. The hospital admission endpoints were modelled separately to capture the appropriate resource use for each admission type and to permit sensitivity analysis on the treatment effect of ivabradine. The base-case analysis was however based on all-cause admission. Admission to hospital after the trial was modelled to be equivalent to the within-trial period and assumed to occur at a constant rate throughout the model irrespective of the ageing population. The manufacturer noted that the inclusion of admissions based on the ageing population would produce a more favourable incremental cost-effectiveness ratio (ICER) for ivabradine and that this potential benefit was not captured in the model.

6.7 The treatment effect of ivabradine on cardiovascular mortality (including heart failure death) was estimated as a hazard ratio of 0.90 (95% CI 0.80 to 1.03) from the parametric model to the underlying mortality risk in the standard care group. Sensitivity analysis was carried out to show the treatment effect of ivabradine on heart failure mortality only. It was assumed that the treatment

effect of ivabradine continues after the trial and is equivalent to that in the SHIFT trial. To support this assumption, the manufacturer highlighted that the heart rate lowering effect of ivabradine was shown to be maintained throughout the SHIFT trial period and also over a 7-year extension period of ivabradine studies in patients with angina. The treatment effect of ivabradine on the rate of admissions to hospital was estimated using a rate ratio of 0.83 (95% CI 0.78 to 0.93) derived from the Poisson regression model. The treatment effect was modelled on all-cause admission because cardiovascular and heart failure admissions were assumed to be implicitly captured in all-cause admission and ivabradine was shown to have a significant effect on all-cause admission in the main trial and licensed populations. The treatment effect of ivabradine on heart failure mortality only was shown in a sensitivity analysis. The length of stay associated with a hospital admission was estimated using external data based on expert clinical advice. In the base-case model, average length of stay was varied according to diagnosis on hospital admission (heart failure: 7.57 days, other cardiovascular: 3.97 days and non-cardiovascular: 5.13 days) and was based on a weighted average of elective and non-elective NHS reference cost data.

6.8 The utility values used in the model were derived from the SHIFT-PRO sub-study in which health-related quality of life was captured with the EQ-5D questionnaire. EQ-5D index scores were calculated using UK population tariff values and then analysed using a mixed regression model. Quality of life was modelled to reflect patients' baseline characteristics, severity of the disease over time by NYHA class, rate of hospital admission (which includes serious adverse events) and treatment group. The resulting utility scores by NYHA class without any hospital admission ranged from 0.82 in class I to 0.46 in class IV. Decrease

in quality of life because of hospital admission was estimated as utility decrements by 0.07, 0.03, 0.08 and 0.21 for NYHA class I, II, III and IV respectively. The effect of ivabradine on quality of life was modelled to show a utility increment of [redacted] in the ivabradine group compared with the baseline estimates used for the standard care group. Treatment-related adverse events were assumed not to have any measurable impact on quality of life and the manufacturer indicated that they have been captured by the treatment covariate in the regression model. The manufacturer applied the utility values from another heart failure study (Gohler et al. 2009) in a sensitivity analysis. Quality of life was assumed to remain the same for each NYHA class in the post-trial period and in the base case and the model estimates were not based on an ageing population. This implies that the utility values for the patients in later cycles were higher than they should be and this was assumed to have favoured ivabradine because additional survival time was associated with greater quality-adjusted life year (QALY) benefits. In a sensitivity analysis, quality of life was adjusted for the increasing age of the modelled cohort by resetting the baseline age for each cycle.

6.9 The average monthly cost of ivabradine (£42.10) used in the model was estimated according to the proportion of patients who received 2.5 mg (7%) and 5 mg or 7.5 mg (93%) in the SHIFT study. The 5 mg and 7.5 mg tablets cost £40.17 per 56-tablet pack each (BNF 63), while the price of the 2.5 mg dose was assumed to be half of the 5 mg tablet. Average monthly standard care costs (£9.54) were estimated according to the proportion of patients using each standard care medication in SHIFT. The unit costs of the standard care drugs used such as beta-blockers, ACE inhibitors, diuretics, aldosterone antagonists, angiotensin receptor blockers and cardiac glycosides were also from the BNF. The manufacturer assumed that there were no extra costs in

administering ivabradine and the standard care drugs. However, additional costs were included for ivabradine therapy titration (specialist visit) and an electrocardiograph (ECG), as a conservative assumption by the manufacturer. This increased the total monthly cost in the ivabradine group from £52 to £202.

Table 4 Unit costs associated with the technology in the economic model (£)

Items	Ivabradine plus standard care	Standard care alone	Source
Technology cost per pack	40.17	–	BNF
Mean cost of technology treatment (per month)	42.10	–	BNF
Mean cost standard care treatment	9.54	9.54	BNF
Administration cost	–	–	–
Specialist visit (one-off)	118.81	–	NHS reference cost
ECG (one-off)	31.28	–	NHS reference cost
Total cost per month (month 1)	**201.73**	**9.54**	
Total cost per month (subsequent months)	**51.64**	**9.54**	

Source: manufacturer's submission (table 54)

6.10 The hospital admission costs used in the model were estimated using the NHS reference cost for heart failure admissions (general ward: £2308 and cardiac ward: £3295), cardiovascular admissions (general ward: £1942 and cardiac ward: £1730) and non-cardiovascular admissions (general ward: £2644). It was assumed that there was an equal probability of being in a general ward or a cardiac ward. Serious adverse events were captured using these hospital admission endpoints, while the non-serious adverse events

were not included. The cost of heart failure management per month which includes physician visits, outpatient procedures and diagnostic tests was estimated to be £27 from British Heart Foundation statistics.

6.11 The base-case results of the economic analysis which was based on the licensed population show that the incremental cost accrued and incremental QALYs gained from treating chronic heart failure with ivabradine plus standard care compared with standard care alone were £2376 and 0.28 QALYs respectively. This resulted in an ICER of £8498 per QALY gained. The manufacturer highlighted that the base-case result was estimated by applying individual patient profiles from SHIFT into the risk equations sequentially, 1 at a time.

Table 5 Base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Standard care	9445.74	3.99	–	–	–
Ivabradine plus standard care	11,821.96	4.27	2376	0.28	8498

Source: manufacturer's submission (table 65)

6.12 The manufacturer highlighted that the deterministic, probabilistic and structural sensitivity analyses were performed using average covariate values in the regression equations because of protracted analysis time and that this may have caused some loss in accuracy in the ICER estimates. The base-case ICER using this method is £7743. The 1-way deterministic sensitivity analyses were performed on several model parameters using their 95% confidence intervals. The cost-effectiveness result was most sensitive to changes in cardiovascular mortality risk with the resulting ICERs ranging from approximately £5600 to £40,600 per

QALY gained. The base-case ICER also showed some sensitivity to changes in the rate of hospital admission (approximately £6400 to £10,400 per QALY gained) and treatment effect of ivabradine on quality of life (approximately £6300 to £9300 per QALY gained). Changes in hospital length of stay and ivabradine treatment effect on NHYA class resulted in much less impact on the ICER, approximately £7000 to £8300 and £7200 to £8300 respectively.

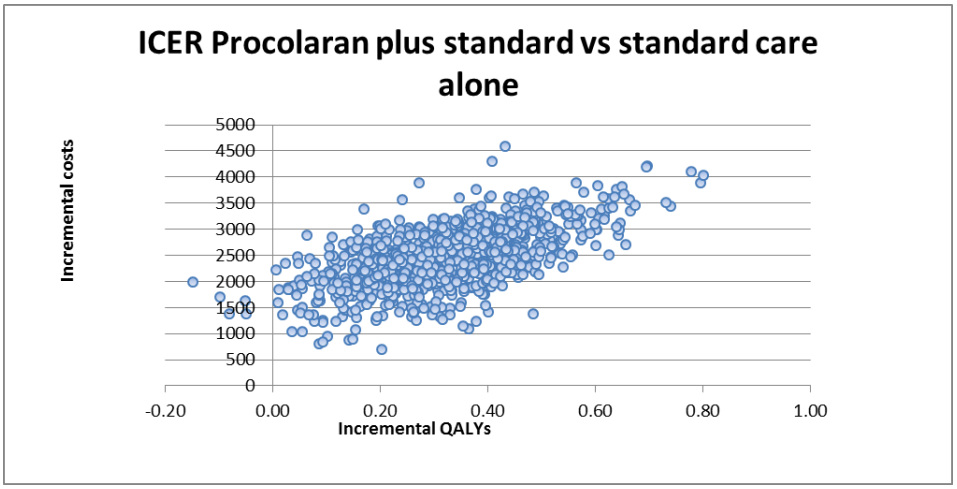
Table 6 One-way deterministic sensitivity analysis

Parameter	ICER – low (£)	ICER – high (£)
Ivabradine hazard ratio cardiovascular mortality	5655	40,638
Ivabradine rate ratio hospital admission	6384	10,424
Ivabradine treatment effect on quality of life	6283	9253
Length of stay in hospital	6938	8549
Ivabradine treatment effect on NYHA class	7232	8349

Source: manufacturer's economic model

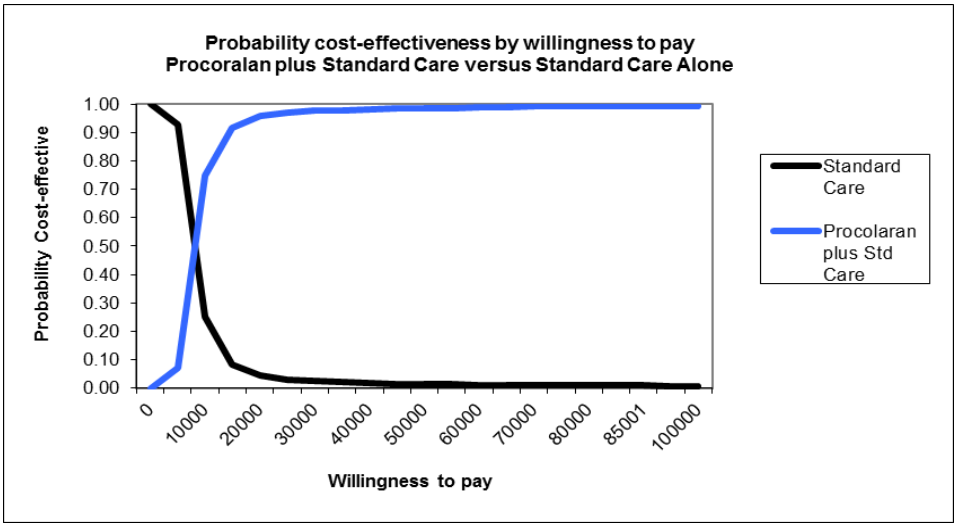
6.13 The probabilistic sensitivity analysis conducted by the manufacturer indicated that ivabradine plus standard care would have a more than 95% chance of being cost-effective compared with standard care alone if the maximum acceptable ICER was £20,000 per QALY gained. The probabilistic sensitivity analysis and cost-effectiveness acceptability curve used to present the results were also based on the average covariate values rather than individual patient profiles in the regression equations.

Figure 2 Probabilistic sensitivity analysis: scatter plot



Source: manufacturer's submission (figure 17)

Figure 3 Cost effectiveness acceptability curve



Source: manufacturer's submission (figure 18)

6.14 The manufacturer also conducted different scenario analyses to manage the uncertainties surrounding some of the assumptions made about the base case model structure. The ICER reduced to £7218 when the ivabradine treatment is stopped after 5 years, in which case the hazard ratio for death becomes 1 and the cost ceases. If a worst-case scenario in which the benefit of ivabradine

reduced linearly to 0 but costs continued was assumed, the ICER increases to approximately £15,078 per QALY gained over 5 years and £13,964 per QALY gained over 10 years. Two alternative parametric survival models (exponential and Weibull) and Kaplan Meier data were used to estimate cardiovascular mortality risk in a scenario analysis and this resulted in ICERs of £7468, £7400 and £8536 per QALY gained respectively. There was little impact on the ICER (approximately £7305 per QALY gained) when the median length of hospital stay was increased to 9 days based on national heart failure audit data rather than 5.13 days from the NHS reference cost data. However, it decreased to £6881 per QALY gained when the costs of titration visit and ECG were excluded from the model. After clarification, the manufacturer provided a scenario analysis in which a new regression equation was developed to predict NYHA class distribution, adjusting for treatment, time covariates and patient baseline characteristics, and BNF drug prices were revised to reflect 2012 estimates. This analysis increased the ICER to £8698.

6.15 The ICER increased to £15,200 per QALY gained when a within-trial time horizon was assumed. But the ICER was insensitive to changes in the data source used for the extrapolation of cardiovascular mortality and utility values. In both scenarios, external data from previous heart failure studies were used in place of the SHIFT data used in the base-case model. Including age-adjusted utility values did not make any significant impact on the ICER (it increased to £7959). The proportion of patients predicted to be in NYHA class II, III and IV by year 15 were 31.1%, 39% and 26.2% respectively in a scenario in which it was assumed that there was a 5% change in the distribution of NYHA classes (from NYHA I to II, from NYHA II to III and from III to IV) in the post-trial period. This assumption resulted in a higher ICER of £8227 per QALY

gained and when the extrapolation was based on SHIFT predicted data, the ICER reduced to £7630. The manufacturer highlighted that the cost effectiveness result was primarily driven by the treatment effect of ivabradine on cardiovascular mortality, hospital admission and the associated cost of care, as well as small improvements in quality of life.

Table 7 Structural sensitivity analyses

Description	Base case	Sensitivity	Base-case ICER (£)	Sensitivity ICER (£)
CV mortality	Gompertz	Kaplan Meier	7743	8536
CV mortality	Gompertz	Weibull	7743	7400
CV mortality	Gompertz	Exponential	7743	7468
CV mortality extrapolation	Gompertz	CARE-HF	7743	7066
CV mortality extrapolation	Gompertz	Australian data	7743	7934
Treatment effect	CV endpoint	HF endpoint	7743	7889
Ivabradine hazard ratio tailing off over 5 years	Lifelong	5 years	7743	15,078
Ivabradine hazard ratio tailing off over 10 years	Lifelong	10 years	7743	13,964
Ivabradine treatment duration	Lifelong	5 years	7743	7218
Length of stay in hospital	NHS reference cost	HES data	7743	6486
Length of stay in hospital	NHS reference cost	NHF audit	7743	7305
NYHA class extrapolation	Last observation	SHIFT predicted	7743	7630
NYHA class extrapolation	Last observation	Assumption based	7743	8227
Quality of life weights	SHIFT predicted	External literature	7743	7538
Quality of life weights: excluding age adjustment	Included	Excluded	7743	7959
Titration visit and ECG costs excluded	Included	Excluded	7743	6881
CARE-HF, cardiac resynchronisation in heart failure; CV, cardiovascular; HF, heart failure; HES, hospital episode statistics; NHF,national heart failure				

Source: manufacturer's economic model

6.16 The manufacturer carried out several subgroup analyses based on individual patient characteristics from the licensed population and the results showed that ivabradine plus standard care remained cost effective when compared with standard care alone. The ICER reduced to £8464 per QALY gained for the group of patients who were younger than 75 years and increased to £9101 per QALY gained for the group aged 75 years and older. The ICERs for the NYHA class II to IV subgroups ranged from £9712 to £5197 per QALY gained, which suggests that it may be more cost effective to treat people with worse prognoses. Ivabradine remained cost-effective across all beta-blocker doses, with ICERs ranging from £5361 per QALY gained with no beta-blockade to £10,374 per QALY gained for the patients taking the target dose of beta-blockers. Other subgroup analyses based on heart failure duration, level of LVEF and prior medical history (coronary artery disease and diabetes) all had ICERs ranging from £6258 to £10,427 per QALY gained. The manufacturer also carried out an additional subgroup analysis based on a population representative of a UK heart failure patient group. This population was specified as western European male with a median age of 78 years and receiving at least half the target dose of beta-blockers. The ICER generated for this subgroup was £8735 per QALY gained while that for the UK heart failure patient group taking the target dose of beta-blocker was £9185 per QALY gained.

Table 8 Results: subgroup analyses

Subgroup	Incremental costs	Incremental QALYs	Incremental cost/QALY
All patients (heart rate 75 bpm or more)	2376	0.280	8498
Aged younger than 75 years	2476	0.293	8464
Aged 75 years or older	1421	0.156	9101
NYHA class II	2744	0.283	9712
NYHA class III	2090	0.280	7467
NYHA class IV	1083	0.208	5197
Heart failure duration <0.6 years	2919	0.329	8886
Heart failure duration ≥0.6, <2 years	2466	0.290	8489
Heart failure duration ≥2, <4.8 years	2318	0.260	8901
Heart failure duration ≥4.8 years	1820	0.240	7573
No beta-blocker	1652	0.308	5361
Beta-blocker < half target dose	2098	0.271	7726
Beta-blocker ≥ half target dose <target dose	2703	0.279	9689
Beta-blocker ≥ target dose	2896	0.279	10374
LVEF < 26%	1785	0.285	6258
LVEF ≥26%, <30%	2185	0.272	8030
LVEF ≥30, <33%	2582	0.284	9090
LVEF ≥33%	2865	0.275	10427
Non-diabetic	2487	0.280	8883
Diabetic	2135	0.279	7654
No prior coronary artery disease	2477	0.318	7785
Prior coronary artery disease	2335	0.264	8851
LVEF, left ventricular ejection fraction			

Source: manufacturer's submission (table 66)

Evidence Review Group comments

6.17 The ERG was satisfied with the manufacturer's modelling approach, which was largely transparent, made use of patient-level data and was consistent with other published economic studies on heart failure treatments. However it stated that the large use of coding made it difficult to stress test the model. The ERG said that the manufacturer did not carry out an analysis in a patient

population with a disease severity reflective of the UK population. However, it agreed with the manufacturer that values for patient characteristics beyond the SHIFT population range may generate unreliable results. The ERG was satisfied that the standard care treatments used in the SHIFT trial and the economic model reflected UK clinical practice.

6.18 The ERG accepted the manufacturer's use of Office for National Statistics UK life tables to provide estimates of the non-cardiovascular mortality in the base case because this is standard practice in heart failure cost-effectiveness analyses, although it noted that the risk was higher in SHIFT than the UK life tables. The ERG noted that there were some uncertainties associated with the regression analyses performed for cardiovascular and heart failure mortality, which limited the potential of ivabradine to reduce the risks of these 2 outcomes. The treatment effect of ivabradine was statistically non-significant for cardiovascular mortality and borderline significant for heart failure, unlike in the clinical trial in which they were significant. By contrast, beta-blockade at 50% or more of the target dose was associated with a statistically significant reduction in the risk of cardiovascular mortality and beta-blockade at any level was associated with a statistically significant reduction in the risk of heart failure mortality. Because baseline heart rate was adjusted for in the regression analysis, the ERG thought that the risk reduction of ivabradine and beta-blockade was over and above the attenuating effect of heart rate.

6.19 The ERG indicated that the regression model for health-related quality of life in the manufacturer's submission was clinically plausible and the disutility associated with hospital admission was likely to have captured any serious impacts of adverse events on

quality of life because hospital admission would be the main consequence of serious adverse events. The ERG noted that the impact of age adjustment for health-related quality of life was minimal (it increased the ICER by £225). Therefore, it accepted the exclusion of age adjustment from the base-case analysis because of the time needed to re-run each cycle to adjust for age throughout the model's time horizon. The ERG was satisfied with the costing approach taken by the manufacturer in the economic analysis.

6.20 The ERG considered that the manufacturer's base-case ICER of £8498 per QALY gained was likely to represent the expected cost-effectiveness of adding ivabradine to standard care, although they believed it was biased against ivabradine. The ERG was satisfied with the manufacturer's pragmatic approach of conducting the sensitivity analyses using average patient characteristics because of the protracted analysis time needed to use individual patient profiles for the base case. It indicated that the reduced level of accuracy with this method was unlikely to alter any conclusions drawn from the evidence presented. The ERG was particularly interested in the cost-effectiveness results in the subgroups of patients at different levels of beta-blockade. It noted that the ICERs for these subgroups and the other subgroups analysed remained below £11,000. However, the ERG noted that the regression equations used were based on the main or licensed population of SHIFT, rather than the particular subgroup of patients considered. It accepted that that the issues of breaking randomisation and smaller patient numbers would compromise any analyses based on regression equations developed from subgroups. The ERG highlighted that the hazard ratios estimated from regression equations based on the main or licensed population of SHIFT may over (or under) estimate the effect of treatment in particular patient populations.

6.21 Overall, the ERG considered the modelled results to be conservative because they underestimated the risk of cardiovascular mortality, the rate of hospital admission and the relative effect of treatment with ivabradine plus standard care compared with standard care alone. It stated that the sensitivity and subgroup analyses sufficiently assessed any areas of uncertainty.

7 Equalities issues

7.1 The patient experts raised a potential equality issue regarding the higher prevalence of non-revascularisable coronary artery disease in the Asian population because of the aggressive nature of diabetes as a risk factor.

8 Innovation

8.1 The manufacturer stated that ivabradine is the only non-surgical treatment available for people with heart failure whose prognosis remains poor after optimised recommended therapy for heart failure. The manufacturer also stated that treating heart failure with ivabradine in addition to standard care results in a statistically significant improvement in health-related quality of life, which no other current treatment has achieved, as shown in published evidence.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. NICE clinical guideline 108 (2010). Available from www.nice.org.uk/guidance/CG108
- Cardiac resynchronisation therapy for the treatment of heart failure. NICE technology appraisal guidance 120 (2007). Available from www.nice.org.uk/guidance/TA120

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120). Earliest anticipated date of publication September 2013.

NICE pathways

- There is a NICE pathway on chronic heart failure, which is available from http://pathways.nice.org.uk/pathways/chronic-heart-failure

Appendix B: clinical efficacy section of the draft European public assessment report

The European public assessment report for ivabradine was first published on 18 July 2006 and updated on 27 March 2012; it is available from:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000597/human_med_000995.jsp&mid=WC0b01ac058001d124