Ivabradine for treating chronic heart failure

Technology appraisal guidance
Published: 28 November 2012

www.nice.org.uk/guidance/ta267

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1   Recommendations

1.1   Ivabradine is recommended as an option for treating chronic heart failure for people:

- with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and

- who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and

- who are given ivabradine in combination with standard therapy including beta-blocker therapy, angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and

- with a left ventricular ejection fraction of 35% or less.

1.2   Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists.

1.3   Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

2 The technology

2.1 Ivabradine (Procoralan, Servier Laboratories) is a heart-rate-lowering agent that selectively and specifically inhibits the cardiac pacemaker If current, which 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 higher, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated'. Ivabradine is administered orally at a recommended starting dose of 5 mg twice daily. This dose may be 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. For full details of dosage see the summary of product characteristics.

2.2 The summary of product characteristics lists the following adverse reactions for ivabradine: luminous phenomena (phosphenes), bradycardia, atrioventricular first degree, ventricular extrasystoles, blurred vision, headache, dizziness and uncontrolled blood pressure. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Ivabradine is available in 5 mg and 7.5 mg tablets at a net price of £40.17 per 56-tablet pack (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 either 5 mg or 7.5 mg (93%) in the SHIFT study (see section 3.1). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The appraisal committee (appendix A) considered evidence submitted by the manufacturer of ivabradine and a review of this submission by the evidence review group (ERG; appendix B).

3.1 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, known as SHIFT (systolic heart failure treatment with the If inhibitor ivabradine trial). 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 trial was carried out in 625 centres in 37 countries and lasted from 12 to 36 months in the active double-blind treatment period, extended to a maximum duration of 52 months. The clinical-effectiveness evidence presented in the manufacturer's submission was based on this trial alone, but results were also provided for the SHIFT patient-reported outcomes (SHIFT-PRO) study. SHIFT-PRO was carried out to evaluate the effects of ivabradine compared with placebo on health-related quality of life in a representative sample of the main trial population.

3.2 Patients with symptomatic heart failure with a left ventricular ejection fraction of 35% or lower who were in sinus rhythm with a heart rate of 70 bpm or more and were receiving stable background treatment for heart failure were considered eligible for participation in SHIFT. After screening, 6,505 patients were randomised to receive either ivabradine or placebo in addition to ongoing optimal therapy (standard care) 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. This dose was maintained, or increased to 7.5 mg twice daily or reduced 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 1,190 patients died, withdrew consent or were lost to follow-up.

3.3 The trial groups in SHIFT were well balanced in patient baseline characteristics. The mean age was 60.4 years, 76% of the patients were men and mostly white. Mean heart rate was 79.9 bpm and mean left ventricular ejection fraction was

29%. Heart failure was ischaemic 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 groups, with less than 20% of the patients being current smokers in both groups. The background therapies were also similar in both arms (ACE inhibitors or angiotensin receptor blockers: 91%; diuretics: 84%; beta-blockers: 89%; aldosterone antagonists: 61% and cardiac devices [implantable cardioverter defibrillators: 3% and cardiac resynchronisation therapy: 1%]).

3.4   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. The manufacturer stated in its submission that another subgroup was identified after the committee for Medicinal Products for Human Use recommended identifying the heart rate threshold at which there is a statistically significant mortality benefit. This subgroup consisted of people with a baseline heart rate of 75 bpm or more (n=4,150) and was identified post hoc. Data from this subgroup were used to identify the population to be covered by the marketing authorisation. 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).

3.5   The baseline characteristics of the subgroup with a baseline heart rate of 75 bpm or more (the population covered by the marketing authorisation) 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 men (77%) and mostly white. There were no baseline differences between the treatment groups in this population including mean heart rate (84.5 bpm) and distribution of NYHA class. The background therapies received were also similar to the main trial population for both treatment groups (ACE inhibitors or angiotensin receptor blockers: 90%; diuretics: 84%; beta-blockers: 88%; aldosterone antagonists: 62% and cardiac devices).

3.6   The primary outcome in the SHIFT main trial population 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 time-to-first event estimated by the Kaplan-Meier method. Secondary and other

efficacy outcomes included mortality, hospital admission, 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).

3.7   In the SHIFT-PRO study (n=5,038), which studied a subset of the main SHIFT population, health-related quality of life was estimated using the EuroQol-5 dimensions (EQ-5D) questionnaire and 'Kansas City cardiomyopathy questionnaire' (KCCQ). Analysis in this 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 patients had received at least half the target dose of beta-blockers at randomisation. The manufacturer's submission noted that there were no relevant differences in baseline demographics and disease characteristics among the main trial population, the population covered by the marketing authorisation and the population in the SHIFT-PRO study.

Main SHIFT population

3.8   In the main trial population, the primary outcome of first event of cardiovascular death or hospital admission for worsening heart failure was analysed using a Cox proportional hazards model adjusted for beta-blocker intake at randomisation. The hazard ratio (HR) estimate was 0.82; (95% confidence interval [CI] 0.75 to 0.90, p<0.0001), representing a statistically significant relative risk reduction of 18% for ivabradine compared with placebo. 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.

3.9   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 of ivabradine compared with placebo 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 (25% or more but less than 50% of target dose)

- HR 0.88; 95% CI 0.72 to 1.07, p=0.193 (50% or more 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 for ivabradine compared with placebo 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.

Population covered by the marketing authorisation

3.10 In the subgroup with a baseline heart rate of 75 bpm or more, the incidence of the primary composite endpoint was statistically significantly lower in the ivabradine group than in 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 endpoint for ivabradine compared with placebo (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.

3.11 There was a statistically significant improvement in all secondary outcomes for the population covered by the marketing authorisation, unlike for the main SHIFT population in whom some of the secondary outcomes were not statistically significant. There were statistically significant reductions in all mortality outcomes in the ivabradine group compared with placebo as follows:

- 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)

- all-cause death (HR 0.83; 95% CI 0.72 to 0.96, p=0.0109).

  Results similarly favoured ivabradine compared with placebo for:

- hospital admission for cardiovascular problems (HR 0.79; 95% CI 0.71 to 0.88, p<0.0001)

- worsening heart failure (HR 0.70; 95% CI 0.61 to 0.80, p<0.0001)

- hospital admission for any cause (HR 0.82; 95% CI 0.75 to 0.90, p<0.0001).

3.12   In the population covered by the marketing authorisation, heart rate decreased in the ivabradine and placebo groups by 17.4 bpm and 5.7 bpm at day 28 and 14.5 bpm, and 5.8 bpm at the last visit respectively. The manufacturer noted that the greater decrease in heart rate in the population covered by the marketing authorisation 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 showed that greater reductions in heart rate are associated with higher resting heart rate. In this subgroup there was a statistically significant improvement in NYHA class in the ivabradine group compared with the placebo group.

3.13   Using the SHIFT-PRO study data, 3 types of quality-of-life analyses were performed. The first (main analysis) used '0' as the last post-baseline value for deceased patients, the second (an analysis of surviving patients) used the last post-baseline value for deceased patients, and the third used the change from baseline to month 12 from the main analysis. For the EQ-5D index score measure, quality of life worsened from baseline to the last assessment in the ivabradine group and the placebo group 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 groups, with a greater improvement in the ivabradine group. The quality of life improvement from baseline to month 12 in both groups was higher in the ivabradine group. The manufacturer suggested that this was because there were fewer deaths during the first 12 months than during the whole study.

3.14   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 improved in the ivabradine group for the population covered by the marketing authorisation. The KCCQ disease-specific measure was also used and it showed a statistically significant difference of 2.6 (95% CI 0.7 to 4.5, p=0.008) for ivabradine compared with placebo for the 12-month analysis, which was also similar to the main analysis and the analysis of surviving patients.

3.15   The safety population (n=6,492 main trial cohort; n=4,141 population covered by the marketing authorisation) was the population 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 population covered by the marketing authorisation: 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. 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 affected by baseline heart rate because there were no differences in the adverse events leading to withdrawal between the main trial population and the population covered by the marketing authorisation.

3.16   After a request from the ERG during the clarification stage, the manufacturer provided the absolute numbers for the primary composite outcome and key secondary outcomes for the subgroups of the population covered by the marketing authorisation according to their beta-blocker category, age and NYHA class (details of the analyses are in section 3.22). The manufacturer also provided separate scenario analyses of the impact of using a regression model for NYHA progression adjusted for patient baseline characteristics, using updated standard care drug costs and different assumptions for modelling mortality. In addition, the manufacturer provided details of the patients who experienced symptomatic bradycardia and atrial fibrillation, and follow-up data on the reduction in heart rate at various time points for the population covered by the marketing authorisation.

Evidence review group comments – population covered by the

marketing authorisation

3.17   The ERG stated that the literature search conducted by the manufacturer was appropriate, all relevant studies had been identified and that SHIFT, 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, it highlighted that only 12 patients (0.2%) in the study were recruited from the UK, but noted the manufacturer's comment about the difficulties gaining study approval in the UK. The ERG also stated that the low UK patient 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 population covered by the marketing authorisation was younger, included a higher proportion of men and patients with more severe heart failure than a typical UK heart failure patient population, but it recognised that the baseline characteristics of the population covered by the marketing authorisation were similar to those reported for other key heart failure studies. However, the ERG considered that the results of SHIFT were robust and generalisable to a UK population because there was evidence to suggest that the patients in the trial received standard treatments.

3.18   The ERG noted that the clinical-effectiveness evidence for 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 marketing authorisation. 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 population covered by the marketing authorisation.

3.19   The ERG was aware that only approximately 26% of the main trial population and the population covered by the marketing authorisation were each treated with the recommended target dose of beta-blocker, and 55.4% of the trial population covered by the marketing authorisation were treated with 50% or more of the recommended dose of beta-blocker 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 also noted the low use of cardiac devices in SHIFT and considered that this could have resulted from the exclusion of patients with pacemakers from the trial.

3.20   The ERG noted that the greatest benefit of ivabradine compared with placebo was in reducing 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 ivabradine was associated with an improvement in NYHA class in the population covered by the marketing authorisation at their last visit compared with their baseline classification and that it had little impact on the proportion of patients with worsening NYHA classification.

3.21   The ERG noted that treatment-related adverse events occurred more frequently in the ivabradine group (17.8%) than in the placebo group (8.3%) in the main trial population. It felt that this was likely to be the same for the population covered by the marketing authorisation 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 left ventricular systolic dysfunction.

3.22   The ERG carried out an exploratory analysis of the data provided by the manufacturer after the clarification request on the primary and secondary outcomes of the population covered by the marketing authorisation according to their beta-blocker dosage at randomisation (that is, no beta-blocker, less than 25% of target beta-blocker dose, 25% or more but less than 50% of target beta-blocker dose, 50% or more but less than 100% of target beta-blocker dose and 100% or more of target beta-blocker dose).The ERG highlighted that their exploratory analyses suggest 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 at least 25% of beta-blockers. The ERG also explored the efficacy of ivabradine according to NYHA class and in patients aged 70 years or older. It noted that the analysis in the NYHA class IV subgroup was based on small numbers, creating uncertainty about the benefit of ivabradine observed in

this subgroup. Because the input data used in the exploratory analyses were marked as academic-in-confidence by the manufacturer, the results have also been marked as confidential and so cannot be shown here. However, the ERG emphasised that these analyses are speculative and based on subgroups of subgroups and should be interpreted with caution.

Cost-effectiveness evidence

3.23   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. No cost-effectiveness data were presented for the main SHIFT population, and so the economic evaluation carried out by the manufacturer was based only on the post hoc subgroup of patients from SHIFT with a baseline heart rate of 75 bpm or more. The manufacturer stated that this subgroup reflected the marketing authorisation 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.

3.24   The manufacturer developed a Markov cohort model consisting of 2 states (alive and dead). The difference in quality of life of patients was 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 in line with SHIFT because the use of heart failure medications in the trial was higher than current standard care treatment patterns in the UK. 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 population covered by the marketing authorisation. This was to avoid breaking randomisation and reducing the predictive power of the risk equations because of smaller sample size. However, the risk equations for mortality, hospital admission and quality of life were adjusted for baseline heart rate to predict estimates for the population

covered by the marketing authorisation with a heart rate of 75 bpm or more.

3.25   The manufacturer estimated the risk of non-cardiovascular death based on age-adjusted and sex-adjusted UK national life table data from the Office for National Statistics rather than SHIFT data because it provided a larger, UK-specific data source. This risk 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 a Gompertz parametric survival regression model based on the full SHIFT cohort in the base-case analysis. Survival models based on exponential and Weibull parametric distributions, and 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. Mortality was approximately 17% in the standard care group of SHIFT. Because 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 the sensitivity analyses. The extrapolation assumed that 50% of the cohort would have died after 2,000 days (65 months).

3.26   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, whereas 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 any 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 were expected to vary according to the number of patients alive).

3.27   The rate of heart failure, cardiovascular and all-cause hospital admission per person month was estimated using a 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. However, the base-case analysis was based on all-cause hospital 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.

3.28   The treatment effect of ivabradine on cardiovascular mortality (including heart failure death) compared with placebo 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. It was assumed that the treatment effect of ivabradine continues after the trial and is equivalent to that seen in SHIFT. To support this assumption, the manufacturer highlighted that the heart-rate-lowering effect of ivabradine was shown to be maintained throughout SHIFT and also over a 7-year study period for ivabradine 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 statistically significant effect on all-cause admission in the main trial and populations covered by the marketing authorisation. The length of stay associated with hospital admission was estimated using external data based on expert clinical advice. In the base-case model, the 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.

3.29   The utility values used in the model were derived from the SHIFT-PRO 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 decreases in utility of 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 and showed a small utility increase in the ivabradine group compared with the baseline estimates used for the placebo (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 had been captured by the treatment covariate in the regression model. 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 the sensitivity analysis, quality of life was adjusted for the increasing age of the modelled cohort by resetting the baseline age for each cycle.

3.30   The average monthly cost of ivabradine (£42.10; excluding VAT) used in the model was estimated according to the proportion of patients who received 2.5 mg (7%) and either 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 (excluding VAT; BNF 63), and the price of the 2.5 mg dose was assumed to be half the price 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 taken 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 (1 specialist visit) and an electrocardiogram (ECG). This increased the total monthly cost in the ivabradine group from £52 to £202 for the first month.

3.31   The hospital admission costs used in the model were estimated using the NHS reference costs for heart failure admissions (general ward: £2,308 and cardiac ward: £3,295), cardiovascular admissions (general ward: £1,942 and cardiac

ward: £1,730) and non-cardiovascular admissions (general ward: £2,644). 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, but non-serious adverse events were not included. The monthly cost of managing heart failure, including physician visits, outpatient procedures and diagnostic tests, was estimated to be £27 from British Heart Foundation statistics.

3.32   The base-case results of the economic analysis, which was based on the population covered by the marketing authorisation, was estimated by applying individual patient profiles from SHIFT to the risk equations sequentially, one at a time. It showed that the incremental costs and incremental QALYs gained from treating chronic heart failure with ivabradine plus standard care compared with standard care alone were £2,376 and 0.28 QALYs respectively. This gave an incremental cost-effectiveness ratio (ICER) of £8,498 per QALY gained.

3.33   The manufacturer highlighted that the deterministic, probabilistic and structural sensitivity analyses were performed using average covariate values in the regression equations to shorten analysis time and that this may have caused some loss in accuracy in the ICER estimates. The base-case ICER using this method was £7,743 per QALY gained. The one-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 £5,655 to £40,638 per QALY gained. The base-case ICER also showed some sensitivity to changes in the rate of hospital admission (£6,384 to £10,424 per QALY gained) and treatment effect of ivabradine on quality of life (£6,283 to £9,253 per QALY gained). Changes in hospital length of stay and ivabradine treatment effect on NYHA class had much less impact on the ICER, £6,938 to £8,549 and £7,232 to £8,349 per QALY gained respectively.

3.34   The manufacturer's probabilistic sensitivity analysis 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.

3.35   The manufacturer carried out different scenario analyses to manage uncertainties

about some of the assumptions in the base-case model. The scenario analyses explored the effect on the ICER of: varying the treatment duration of ivabradine; ivabradine's treatment effect stopping after 5 and 10 years; using alternative models to estimate the risk of cardiovascular mortality; increasing the median length of hospital stay based on the 'National heart failure audit' data; and excluding the costs of the titration visit and the ECG. The manufacturer also carried out other scenario analyses, including: using a within-trial time horizon; using external data to extrapolate cardiovascular mortality and utility values; including age-adjusted utility values; and assuming a 5% change in the distribution of NYHA classes (from I to II, from II to III and from III to IV) in the post-trial period. After a clarification request, the manufacturer also provided a scenario analysis in which a new regression equation was developed to predict NYHA class distribution. This was adjusted for treatment, time covariates and patient baseline characteristics, and drug prices were updated to those in BNF 63. These scenario analyses all gave ICERs below £9,000 per QALY gained except for the assumptions of the treatment effect of ivabradine stopping after 5 and 10 years and using the within-trial time horizon, which gave ICERs ranging from £13,964 to £15,200 per QALY gained.

3.36 The manufacturer carried out several subgroup analyses based on individual patient characteristics from the population covered by the marketing authorisation. These subgroups were based on age, NYHA class, beta-blocker doses, heart failure duration, level of left ventricular ejection fraction, and prior medical history (coronary artery disease and diabetes). The results showed that ivabradine plus standard care was still cost effective when compared with standard care alone. The estimated ICERs for the subgroups were all below £11,000 per QALY gained and ranged from £5,197 to £10,427 per QALY gained. The manufacturer also carried out additional subgroup analyses based on a population representative of a UK chronic heart failure patient group. This population was specified as western European men with a median age of 78 years, receiving at least half the target dose of beta-blockers. The ICER generated for this subgroup was £8,735 per QALY gained, and the ICER for a UK chronic heart failure patient group taking the target dose of beta-blockers was £9,185 per QALY gained.

Evidence review group comments

3.37   The ERG was satisfied with the manufacturer's modelling approach, which was transparent, used patient-level data and was consistent with other published economic studies on heart failure treatments. The ERG stated 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 using values for patient characteristics beyond the SHIFT population range may generate unreliable results. The ERG was satisfied that the standard care treatments used in SHIFT and the economic model reflected UK clinical practice.

3.38   The ERG accepted the manufacturer's use of Office for National Statistics UK life tables to provide estimates of non-cardiovascular mortality in the base case because this is standard practice in heart failure cost-effectiveness analyses. However, it noted that the risk of non-cardiovascular mortality was higher in SHIFT than in 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 in the regression analysis was not statistically significant for cardiovascular mortality (p=0.38) and was borderline statistically significant (p=0.06) for heart failure mortality (although these results had been statistically significant for the population covered by the marketing authorisation only). By contrast, beta-blockers given at 50% or more of the target dose were associated with a statistically significant reduction in the risk of cardiovascular mortality for ivabradine compared with placebo and beta-blockers at any dose were associated with a statistically significant reduction in the risk of heart failure mortality for ivabradine compared with placebo. Because baseline heart rate was adjusted for in the regression analysis, the ERG thought that the risk reduction of ivabradine and beta-blockers was in addition to the attenuating effect of heart rate.

3.39   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 impact 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 £216 per QALY gained). 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.

3.40   The ERG considered that the manufacturer's base-case ICER of £8,498 per QALY gained (incremental costs of £2,376 and incremental QALYs of 0.28) was likely to represent the expected cost effectiveness of adding ivabradine to standard care, although the ERG 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 longer 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 for the subgroups of patients at different doses of beta-blockers. It noted that the ICERs for these subgroups and all other subgroups analysed remained below £11,000 per QALY gained. However, the ERG noted that the regression equations used were based on the main trial population of SHIFT or the population covered by the marketing authorisation, rather than the particular subgroups of patients considered. It accepted that 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 trial population of SHIFT or the population covered by the marketing authorisation may over (or under) estimate the effect of ivabradine treatment in particular patient populations.

3.41   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 addressed any areas of uncertainty.

3.42   Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of ivabradine, having considered evidence on the nature of chronic heart failure and the value placed on the benefits of ivabradine by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.2 The committee considered the clinical need for treatment in people with heart failure who are covered by the marketing authorisation of ivabradine. The committee noted that the clinical specialists indicated that ivabradine is primarily a heart-rate-lowering drug for people with left ventricular systolic dysfunction who are in sinus rhythm and for whom beta-blockers are not suitable. The committee heard from the clinical specialists that people with chronic heart failure have a poor quality of life. It also noted the comment from the patient experts that chronic heart failure can impact on everyday tasks, with comorbidities increasing the impact of the disease and usually requiring lifestyle changes. The patient experts also stated that ivabradine may provide symptomatic and prognostic benefit in a small number of chronic heart failure patients unable to take beta-blockers. The committee considered the clinical specialists' comment that it may be difficult to increase beta-blocker dosage for people with low blood pressure, a group who would benefit from ivabradine. It noted that ivabradine is contraindicated in severe hypotension (less than 90/ 50 mmHg). The committee recognised the impact of chronic heart failure on quality of life and concluded that there were potential treatment benefits with ivabradine for people who are covered by the marketing authorisation.

4.3 The committee considered the generalisability of the SHIFT trial to UK clinical practice. The committee was aware that the population covered by the marketing authorisation in SHIFT was younger, included a higher proportion of men and people with more severe chronic heart failure than the typical chronic heart failure population in the UK. It also noted that only a few people from the UK were

included in the trial and the use of cardiac devices in the trial was low. The clinical specialists and the ERG indicated that the differences in age and severity of chronic heart failure may be caused by patient recruitment from specialist heart failure centres, which is common with randomised trials. The committee considered the comments from the clinical specialists and the ERG that the results of the trial could be extrapolated to a UK setting because the standard therapies used in SHIFT could be regarded as optimal and were given at similar dosing levels to UK clinical practice. Despite the differences between the trial and the UK population, the committee concluded that SHIFT was relevant to UK clinical practice.

4.4   The committee examined the clinical evidence from SHIFT, which compared ivabradine plus standard care with standard care plus placebo. The committee noted that it was a well-conducted clinical trial and that the relevant clinical outcomes of mortality and hospital admission were assessed. It also noted that health-related quality of life data were collected in SHIFT-PRO using both generic and disease-specific instruments, and was aware that improved quality of life was an important outcome for chronic heart failure patients and that this is considered to be one of the main aims of managing chronic heart failure. The committee noted that the committee for Medicinal Products for Human Use had asked the manufacturer to identify the heart rate threshold at which there was a significant mortality benefit with ivabradine, because this benefit was not observed in the main SHIFT population. So the manufacturer then examined a post hoc subgroup of people with a baseline resting heart rate of 75 bpm or more, and this subgroup formed the population for whom ivabradine has a marketing authorisation. The committee noted that the results from this subgroup demonstrated a statistically significant reduction in all primary and secondary endpoints assessed. This included cardiovascular death, which reduced by 17% with ivabradine compared with placebo, unlike in the main SHIFT population, in which the 9% reduction in cardiovascular death was not statistically significant. The committee was aware that baseline resting heart rate was not a stratification factor at randomisation and that this subgroup was identified post hoc, but it was also aware that recommendations could only be made within ivabradine's marketing authorisation. The committee concluded that SHIFT was well conducted and there was it was plausible biologically that a statistically significant mortality benefit will be observed in the subgroup of people with a baseline resting heart rate of 75 bpm or more, which reflects the marketing

authorisation of ivabradine. However they were aware the evidence presented should be interpreted with a level of caution because the subgroup was identified post hoc.

4.5   The committee noted that a previous hospital admission for worsening heart failure in the past 12 months was an inclusion criterion for SHIFT. The committee agreed that this was an important consideration because people with a prior hospital admission in the past 12 months may have more severe chronic heart failure than would be observed in clinical practice, with a higher risk of further hospitalisations, which was the key driver of the clinical and cost-effectiveness estimates. The committee noted that the marketing authorisation for ivabradine depended on the efficacy of ivabradine in a specific post hoc subgroup with more severe heart failure (with a baseline heart rate of 75 bpm or more) to demonstrate a cardiovascular mortality benefit. The committee heard from the clinical specialists that prior hospital admission should not be a factor for considering ivabradine treatment because there are no data to prove that the efficacy of ivabradine is limited to the population who have been admitted to hospital in the previous 12 months. The clinical specialists also highlighted that people had to be stabilised for 4 weeks on standard therapy as an entry criterion into the trial. The committee considered that prior hospital admission did not affect mortality and the marketing authorisation did not make any reference to prior admission status. The committee was aware that ivabradine was contraindicated for people with unstable heart failure. Therefore when discussing ivabradine, it understood it could only be initiated after prior stabilisation therapy. The committee concluded that all people for whom treatment with ivabradine is suitable, according to the marketing authorisation, should be able to receive ivabradine regardless of hospital admission status, but that people should be stabilised for 4 weeks on standard therapy first.

4.6   The committee considered the adverse event profile associated with ivabradine plus standard care compared with placebo plus standard care. The committee noted that symptomatic bradycardia, atrial fibrillation and phosphenes occurred more frequently in the ivabradine group compared with the placebo group, although other serious adverse events were higher in the placebo group. It noted the comments from the clinical specialists that phosphenes are recognised adverse effects of ivabradine, which usually resolve in most patients during treatment. The clinical specialists also stated that ivabradine appeared to be

much simpler and safer to use compared with most heart failure drugs. The committee was concerned that an unusually high proportion of people in the population covered by the marketing authorisation who received a beta-blocker were not treated with the target dose because of hypotension, especially because the mean systolic blood pressure in the population covered by the marketing authorisation was 121 mmHg. It also noted that it would be unusual for people with heart failure to have hypotensive symptoms with this level of blood pressure. It noted the ERG's comment that it has been reported that only 3% to 5% of patients eligible for treatment with beta-blockers are unable to tolerate them because of hypotension or bradycardia. The committee concluded that ivabradine plus standard care had a manageable adverse event profile in the population covered by the marketing authorisation.

4.7 The committee examined the exploratory analysis performed by the ERG on the efficacy of ivabradine according to beta-blocker dose received by the population covered by the marketing authorisation in SHIFT. The committee noted the impact of the beta-blocker doses on the effectiveness of ivabradine, particularly in terms of cardiovascular mortality. However, the committee agreed that this analysis was based on subgroups of a subgroup and should be interpreted with caution. The clinical specialists stated that these results further highlight the need for beta-blockers to be used at optimal doses before ivabradine is initiated, because there is good evidence that beta-blockers reduce cardiovascular mortality at optimal doses. They also emphasised that ivabradine would be less effective in people with chronic heart failure who are optimally treated with beta-blockers because both treatments are primarily heart-rate-lowering agents, although beta-blockers are known to have additional effects beyond their heart-rate-lowering properties. The committee concluded that, given the results of these exploratory analyses, the effectiveness of ivabradine with increasing beta-blocker doses is uncertain.

4.8 The committee also discussed the exploratory analysis performed according to NYHA class by the ERG for the population covered by the marketing authorisation. It heard from the clinical specialists that it was debatable whether the NYHA class IV subgroup could be considered to be in a stable condition given the severity of their heart failure and that ivabradine is contraindicated in unstable heart failure. The committee also heard from the clinical specialists that the benefit observed in this subgroup of people would be expected because they

are the population with the greatest risk of cardiovascular mortality. However, the committee noted that the analysis in this subgroup of people with NYHA class IV heart failure was based on small numbers, which limits the robustness of the results. Therefore the committee concluded that the effectiveness of ivabradine in people with NYHA class IV heart failure was uncertain because of the small patient numbers in the analysis, which meant that these people could not be considered separately as a subgroup.

4.9   The committee discussed the position of ivabradine in the treatment pathway for chronic heart failure, noting that it is indicated in chronic heart failure NYHA class II to IV with systolic dysfunction, for people in sinus rhythm whose heart rate is 75 bpm or more, and in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. The committee heard from the clinical specialists that ACE inhibitors, beta-blockers and aldosterone antagonists used routinely for managing chronic heart failure should always be the initial treatments, because there is robust evidence that they are effective in managing chronic heart failure and improving survival. The clinical specialists all agreed that ivabradine is an additional therapy for a subset of people with chronic heart failure who are in sinus rhythm, and not as a replacement for the recommended standard therapies such as ACE inhibitors, beta-blockers and aldosterone antagonists. They suggested that ivabradine should be considered only when patients are still symptomatic after being stabilised on optimal initial standard therapies at maximally tolerated doses, or when beta-blockers are contraindicated or not tolerated. The clinical specialists expressed their concerns that introducing ivabradine earlier than specified in the marketing authorisation would limit efforts to optimise the use of other standard drugs, particularly beta-blockers. They stressed the need for enough time to titrate beta-blockers to optimal doses according to the 'start low, go slow' recommendations in NICE's guideline on chronic heart failure. The committee concluded that ivabradine should be initiated only after standard treatment with ACE inhibitors, beta-blockers and aldosterone antagonists has been optimised.

4.10   The committee explored what optimising standard therapy with beta-blockers meant in clinical practice. It heard from clinical specialists that it can take several months to appropriately titrate beta-blockers to the optimal dose for a patient. The committee was aware that to optimise and ensure adherence to beta-blocker therapy, continuous monitoring and education and support of the patient by

members of the heart failure multidisciplinary team are needed. The committee also noted comments from consultees and commentators that there have been misconceptions that beta-blockers are contraindicated in, for example, the elderly, or in people with non-reversible chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease or erectile dysfunction. It noted that, in line with NICE's guidance on chronic heart failure, these groups of people should receive beta-blockers. The committee re-emphasised their conclusion in section 4.9 on the importance of optimising beta-blockers before initiating ivabradine.

4.11   The committee also considered the comments from consultees and commentators that there is a recent analysis that shows that digoxin may confer benefits similar to ivabradine for patients in sinus rhythm and with heart failure caused by left ventricular systolic dysfunction. However, the committee noted that digoxin was not included as a comparator in the scope for this appraisal and there was no evidence to support its benefit in this population. The committee concluded that considering digoxin as a comparator to ivabradine is beyond the scope of this appraisal.

4.12   The committee also considered the position of cardiac devices, particularly cardiac resynchronisation therapy, in the treatment pathway for chronic heart failure because the manufacturer proposed positioning ivabradine before them. The clinical specialists were uncertain about this and proposed several different options about the most appropriate choice if people still have symptoms after they are treated with ACE inhibitors, beta-blockers and aldosterone antagonists. The committee noted that very few patients in SHIFT received cardiac resynchronisation therapy. It therefore considered that more evidence would be useful to determine the position of ivabradine in relation to cardiac devices, particularly cardiac resynchronisation therapy, in the treatment pathway. However, the clinical specialists said that choosing whether to treat with ivabradine or cardiac resynchronisation therapy will depend on clinical need and that ivabradine will only be considered if the person is in sinus rhythm as indicated in ivabradine's marketing authorisation. The committee was aware that ivabradine is contraindicated in people whose heart rate is dependent on a pacemaker. The committee recognised that there was some uncertainty about the appropriate choice of treatment when people are eligible for both ivabradine and cardiac resynchronisation therapy, and concluded that the decision will likely

be based on the judgement of the treating clinician.

4.13   The committee considered the comments from the consultees and commentators that ivabradine should only be given to people with a left ventricular ejection fraction of 35% or less. It noted that the patients in SHIFT had left ventricular systolic dysfunction, which was associated with an ejection fraction of 35% or less, and it was aware that this was an entry criterion for the trial. The committee was aware that an ejection fraction level was not specified in the marketing authorisation for ivabradine. However, it considered that ivabradine could not be recommended in people with an ejection fraction that is above 35% because there is no evidence of its effectiveness in that group. The committee discussed how the ejection fraction level will be determined in clinical practice and whether the required tests will be readily available to people who will potentially benefit from ivabradine. It heard that ejection fraction level is usually demonstrated with an echocardiogram and additional tests will not necessarily be required before initiating ivabradine. Therefore, the committee concluded that ivabradine should only be initiated in people with a left ventricular ejection fraction of 35% or less, normally shown on an echocardiogram.

4.14   The committee considered how ivabradine will be prescribed in clinical practice. It heard from clinical specialists that a heart failure specialist in secondary care with access to a multidisciplinary team should initiate ivabradine. The clinical specialists also stated that titration and monitoring of ivabradine could then take place in primary care by a GP with a special interest in heart failure or a heart failure specialist nurse, supported by a multidisciplinary team. They highlighted that this may help ensure the appropriate patients are treated with ivabradine after optimising treatment and stabilising patients on maximally tolerated doses of ACE inhibitors, beta-blockers and aldosterone antagonists. However, the manufacturer anticipated that ivabradine would be prescribed by a clinician experienced in managing chronic heart failure as recommended in the summary of product characteristics. The committee discussed the emergence of increasing heart failure expertise outside secondary care. It noted that NICE's guideline on chronic heart failure defined a specialist as a physician with a subspecialty interest in the management of heart failure and who leads a specialist multidisciplinary heart failure team of professionals with appropriate competencies from primary and secondary care. The committee concluded that ivabradine should be initiated by a heart failure specialist (in line with the NICE

clinical guideline) with access to a multidisciplinary heart failure team and dose titration and monitoring should then be carried out by a heart failure specialist or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

Cost effectiveness

4.15   The committee considered the manufacturer's economic model and the ERG's critique of this model. The committee was aware that the manufacturer had based the economic evaluation on the subgroup of patients with a baseline resting heart rate of 75 bpm or more. The committee noted that this was the subgroup for whom ivabradine has a UK marketing authorisation. The committee concluded that the appropriate population for the economic evaluation of ivabradine for treating chronic heart failure had been captured in the model.

4.16   The committee discussed the assumptions made by the manufacturer in developing the economic model. The committee noted the ERG's comment that the manufacturer's model was transparent and made use of patient-level data in the base-case analysis. It agreed with the ERG that the standard care treatments used in the economic model reflected UK clinical practice. The committee was satisfied that the utility values applied in the model were derived from SHIFT, which was the pivotal trial used in the economic analysis, and considered the approach taken by the manufacturer to obtain the final utility estimates to be plausible and robust. The committee was also satisfied with the costs used by the manufacturer and that the clinical inputs to the model reflected UK practice. The committee was aware that the sensitivity analyses conducted by the manufacturer were robust for the base-case estimate, except for the risk of cardiovascular mortality (see section 3.33 and 3.35), and that the ICERs for all the subgroup analyses were below £11,000 per QALY gained. The committee concluded that the manufacturer's model was robust and the assumptions were realistic and conservative.

4.17   The committee considered the uncertainty around the benefit of ivabradine on cardiovascular mortality given that the ICER ranged between approximately £5,600 and £40,600 per QALY gained when the risk of cardiovascular mortality was varied using the 95% confidence interval around the mean from the trial

data. The committee noted the ERG's comments that there were uncertainties associated with the regression analyses for cardiovascular and heart failure mortality used in the economic model presented by the manufacturer. The committee noted that the treatment effect of ivabradine in the regression analysis had a p value of 0.38 for cardiovascular mortality and a p value of 0.06 for heart failure mortality. For the population covered by the marketing authorisation in the clinical effectiveness analysis, the p value for cardiovascular mortality was 0.02, and for heart failure mortality was less than 0.01. On the other hand, beta-blockers given at 50% or more of the target dose were associated with a statistically significant reduction in the risk of cardiovascular mortality, and beta-blockers at all doses were associated with statistically significant reductions in the risk of heart failure mortality. The committee considered that this further highlights the importance of optimising beta-blocker therapy before treatment with ivabradine. However, the committee noted the ERG's comment that the absence of a statistically significant effect with ivabradine in the model may be a result of the adjustment of patient characteristics not accounted for in the clinical analysis. The committee was also aware that the manufacturer's regression analyses were conservative in favour of placebo, which made the analyses likely to underestimate the risks of cardiovascular and heart failure mortality, and so generated different results from those observed in the population covered by the marketing authorisation of the SHIFT trial. The committee concluded that the additional treatment effect of ivabradine was uncertain compared with the effect of beta-blocker doses.

4.18　The committee considered whether the base-case ICER of approximately £8,500 per QALY gained (incremental cost of approximately £2,400 and incremental QALY of 0.28) of adding ivabradine to standard care estimated by the manufacturer was the most plausible ICER. The committee considered that the ICER suggested that ivabradine was cost effective if a threshold of £20,000 per QALY gained was applied. The committee considered that the effect of ivabradine on the hospital admission endpoints was the key driver of the cost effectiveness of ivabradine plus standard care compared with standard care alone. It noted that ivabradine plus standard care was more effective and cost more than standard care. Additionally it noted that ivabradine was still accruing more QALYs when the confidence interval for the hazard ratio for mortality crossed 1 and favoured standard care alone in the model, which suggested that ivabradine has a large impact in reducing hospital admissions. The committee

agreed that the wide range of sensitivity and subgroup analyses conducted by the manufacturer sufficiently addressed any areas of uncertainty in the economic analysis, including the beta-blocker subgroups, and all produced ICERs below £11,000 per QALY gained. It also considered that the modelled results and most of the model assumptions were conservative and biased against ivabradine. The committee therefore concluded that the manufacturer's ICER estimate of approximately £8,500 per QALY gained was plausible and was likely to represent the expected cost effectiveness of adding ivabradine to standard care for treating chronic heart failure in the population covered by the marketing authorisation.

4.19   The committee recognised the novel mode of action of ivabradine as a heart-rate-lowering agent for patients in sinus rhythm for whom beta-blockers are contraindicated or not tolerated. It also considered the manufacturer's comment that ivabradine is the only non-surgical treatment available for people with chronic heart failure whose prognosis remains poor after recommended optimised therapy for chronic heart failure. However, the committee considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations. The committee therefore concluded that the innovative aspects of ivabradine were already incorporated in the economic model and analyses.

4.20   The committee discussed potential equality issues and gave particular consideration to avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity. The committee noted the potential equality issue raised by the patient experts about the higher prevalence of non-revascularisable coronary artery disease in the Asian population because of the impact of diabetes as a risk factor. It highlighted that higher prevalence rates are not an equality issue that technology appraisal guidance can address. Nevertheless, the committee did not consider that the wording of the recommendations affected access to treatment by this group. The committee also noted that older people and women were under-represented in SHIFT. But it considered that the recommendation for ivabradine was not based on sex or age, does not vary according to the sex or age of the patient, and that all patients would benefit from ivabradine. The committee considered that these were not equality issues under the legislation. The committee therefore concluded that its

recommendations do not have a particular impact on any of the groups whose interests are protected by the legislation and that there is no need to alter or add to its recommendations.

4.21   Overall the committee considered the effectiveness of ivabradine in the subgroup of patients with a resting heart rate of 75 bpm or more derived from SHIFT, the generalisability of the trial to UK clinical practice, the adverse event profile of ivabradine, the position of ivabradine in the treatment pathway of chronic heart failure (that is after optimisation on standard care therapy with ACE inhibitors, beta-blockers and aldosterone antagonists) and the way ivabradine will be prescribed in clinical practice. It also considered the robustness of the economic model, the realistic nature of the assumptions used in the model, the plausibility of the base-case ICERs and the range of sensitivity analyses presented by the manufacturer. The committee noted that there were uncertainties associated with the effectiveness of ivabradine with increasing beta-blocker doses. However, it was convinced of the benefits of adding ivabradine to the standard care therapies for chronic heart failure in the group of people covered by the marketing authorisation. The committee therefore concluded that ivabradine could be considered a cost-effective use of NHS resources for treating chronic heart failure in people covered by the marketing authorisation.

Summary of appraisal committee's key conclusions

Key conclusion

- Sections 1.1, 4.9 and 4.21: The committee recommended ivabradine for treating chronic heart failure having concluded that it could be considered a cost-effective use of NHS resources for treating chronic heart failure, but noted that ivabradine should only be initiated after optimal standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists, and after a stabilisation period on these therapies of 4 weeks.

Current practice

Clinical need of patients, including the availability of alternative treatments

- Section 4.2: Ivabradine is primarily a heart-rate-lowering drug for people with left ventricular systolic dysfunction who are in sinus rhythm and for whom beta-blockers are not suitable. People with chronic heart failure have a poor quality of life and the condition can impact on everyday tasks, with comorbidities increasing the impact of the disease and usually requiring lifestyle changes. The committee recognised the impact of chronic heart failure on quality of life and concluded that there were potential treatment benefits with ivabradine for people who are covered by the marketing authorisation.

The technology

How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?

- Sections 2.1 and 4.2: Ivabradine is a heart-rate-lowering agent that selectively and specifically inhibits the cardiac pacemaker I_f current, which controls the spontaneous diastolic depolarisation in the sinus node that regulates the heart rate. Ivabradine is primarily a heart-rate-lowering drug for people with left ventricular systolic dysfunction who are in sinus rhythm and for whom beta-blockers are not suitable.

- Section 4.19: The committee considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations, and therefore concluded that the innovative aspects of ivabradine were already incorporated in the economic model and analyses.

What is the position of the treatment in the pathway of care for the condition?

- Section 2.1: Ivabradine has a marketing authorisation for people 'in chronic heart failure NYHA class II to IV with systolic dysfunction, who are in sinus rhythm and whose heart rate is ≥75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated'.

- Section 4.9: The committee concluded that ivabradine should be initiated only after optimal treatment with ACE inhibitors, beta-blockers and aldosterone antagonists has

been achieved.

Adverse reactions

- Section 4.6: Symptomatic bradycardia, atrial fibrillation and phosphenes occurred more frequently in the ivabradine group compared with the placebo group, although other serious adverse events were higher in the placebo group. The committee concluded that ivabradine plus standard care had a manageable adverse event profile in the population covered by the marketing authorisation.

Evidence for clinical effectiveness

Availability, nature and quality of evidence

- Section 4.4: The committee noted that SHIFT was a well-conducted clinical trial and that the relevant clinical outcomes of mortality and hospital admission were assessed.

Relevance to general clinical practice in the NHS

- Section 4.3: The results of the SHIFT trial could be extrapolated to a UK setting because standard therapies were used in the trial. Therefore, the committee concluded that SHIFT was relevant to clinical practice in the UK despite the differences between the trial and the UK population.

Uncertainties generated by the evidence

- Sections 4.7 and 4.8: The committee concluded that the effectiveness of ivabradine with increasing beta-blocker doses is uncertain, and also that the effectiveness of ivabradine in people with NYHA class IV heart failure was uncertain because of the small patient numbers.

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?

- Section 4.4: The committee concluded that SHIFT was well conducted and that it was biologically plausible that a statistically significant mortality benefit will be observed in the subgroup of people with a baseline resting heart rate of 75 bpm or more, which

reflects the marketing authorisation of ivabradine. However they were aware the evidence presented should be interpreted with a level of caution because the subgroup was identified post hoc.

- Sections 4.7 and 4.8: The committee concluded that the effectiveness of ivabradine with increasing beta-blocker doses is uncertain, and also that the effectiveness of ivabradine in people with NYHA class IV heart failure was uncertain because of the small patient numbers, given the results of the exploratory analyses on the efficacy of ivabradine according to the beta-blocker dose received and NYHA class in the population covered by the marketing authorisation in the SHIFT trial.

Estimate of the size of the clinical effectiveness including strength of supporting evidence

- Section 4.4: The committee noted that the results from the population covered by the marketing authorisation demonstrated a statistically significant reduction in cardiovascular death of 17% with ivabradine compared with placebo, unlike the main SHIFT population, in which there was a non-significant reduction in cardiovascular death of 9%.

Evidence for cost effectiveness

Availability and nature of evidence

- Section 3.24: The manufacturer developed a Markov cohort model to evaluate the cost effectiveness of ivabradine in combination with standard therapy including beta-blockers, or for whom beta-blockers are contraindicated or not tolerated for treating chronic heart failure.

Uncertainties around and plausibility of assumptions and inputs in the economic model

- Section 4.17: The committee considered the uncertainty around the benefit of ivabradine on cardiovascular mortality given that the ICER ranged between approximately £5600 and £40,600 per QALY gained when the risk of cardiovascular mortality was varied using the 95% confidence interval around the mean from the trial data, and concluded that the additional treatment effect of ivabradine was uncertain compared with the effect of beta-blocker doses.

Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

- Section 4.16: The committee was satisfied that the utility values applied in the model were derived from SHIFT, which was the pivotal trial used in the economic analysis, and considered the approach taken by the manufacturer to obtain the final utility estimates to be plausible and robust.

- Section 4.19: The committee considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations.

Are there specific groups of people for whom the technology is particularly cost effective?

- Section 4.16: The committee was aware that the sensitivity analyses conducted by the manufacturer were robust for the base-case estimate, except for the risk of cardiovascular mortality and the ICERs for all the subgroup analyses were below £11,000 per QALY gained.

What are the key drivers of cost effectiveness?

- Section 4.18: The committee considered that the effect of ivabradine on the hospital admission endpoints was the key driver of the cost effectiveness of ivabradine plus standard care compared with standard care alone.

Most likely cost-effectiveness estimate (given as an ICER)

- Section 4.18: The committee concluded that the manufacturer's ICER estimate of approximately £8500 per QALY gained was plausible and was the most likely cost effectiveness estimate of ivabradine in addition to standard care for treating chronic heart failure in the population covered by the marketing authorisation.

Equalities considerations and social value judgements

- Section 4.20: The committee noted the potential equality issue raised by the patient experts about the higher prevalence of non-revascularisable coronary artery disease in the Asian population because of the impact of diabetes as a risk factor. The

committee also noted that older people and women were under-represented in the SHIFT trial. The committee considered that these were not equality issues under the legislation. It concluded that its recommendations do not have a particular impact on any of the groups whose interests are protected by the legislation and that there is no need to alter or add to its recommendations.

5 Implementation

5.1 [Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has chronic heart failure and the doctor responsible for their care thinks that ivabradine is the right treatment, it should be available for use, in line with NICE's recommendations.

Appendix A: Appraisal committee members, and NICE project team

Appraisal committee members

The appraisal committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. There are 4 appraisal committees, each with a chair and vice chair. Each appraisal committee meets once a month, except in December when there are no meetings. Each committee considers its own list of technologies, and ongoing topics are not moved between committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Gary McVeigh

Vice Chair of Appraisal Committee C, Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr David Black

Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden

Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett

Director for Health Improvement and Medical Director, NHS Barnet, London

David Chandler

Lay member

Dr Mary Cooke

Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

Dr Chris Cooper

General Practitioner, St John's Way Medical Centre, London

Professor Peter Crome

Consultant Geriatrician and Professor of Geriatric Medicine, Keele University

Dr Maria Dyban

General Practitioner, Kings Road Surgery, Glasgow

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell

Consultant in Public Health, Bradford and Airedale Primary Care Trust

Dr Wasim Hanif

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Professor Cathy Jackson

Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler

Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

Ms Emily Lam
Lay member

Dr Grant Maclaine
Director, Health Economics & Outcomes Research, BD, Oxford

Henry Marsh
Consultant Neurosurgeon, St George's Hospital, London

Professor Eugene Milne
Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr Anna O'Neill
Deputy Head of Nursing & Healthcare School/Senior Clinical University Teacher, University of Glasgow

Professor Katherine Payne
Professor of Health Economics, University of Manchester

Dr Martin Price
Head of Outcomes Research, Janssen-Cilag, Buckinghamshire

Dr Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Alan Rigby
Senior Lecturer and Chartered Statistician, University of Hull

Dr Surinder Sethi
Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington

Dr John Stevens
Lecturer in Bayesian Statistics in Health Economics, School of Health and Related

Research, Sheffield

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Dr Judith Wardle
Lay member

NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Nwamaka Umeweni
Technical Lead

Bhash Naidoo/Kay Nolan
Technical Adviser

Lori Farrar
Project Manager

Appendix B: Sources of evidence considered by the committee

The evidence review group (ERG) report for this appraisal was prepared by BMJ Technology Assessment Group:

- Edwards SJ, Barton S, Nherera L, Trevor N, Hamilton V (2012). Ivabradine for the treatment of chronic heart failure: A Single Technology Appraisal. BMJ-TAG, London.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). The manufacturer/sponsor was also invited to make written submissions. Professional/specialist and patient/carer groups and other consultees had the opportunity to give their expert views and, along with the manufacturer/sponsor, also have the opportunity to appeal against the final appraisal determination.

- Manufacturer/sponsor:

  — Servier Laboratories

- Professional/specialist and patient/carer groups:

  — South Asian Health Foundation

  — British Association for Nursing in Cardiac Care

  — British Cardiovascular Society

  — British Heart Foundation

  — British Society for Heart Failure

  — Royal College of Nursing

  — Royal College of Physicians

- Other consultees:

  — Department of Health

- NHS Devon

- Welsh Government

- Commentator organisations (did not provide written evidence and without the right of appeal):

  - Commissioning Support Appraisals Service

  - Department of Health, Social Services and Public Safety for Northern Ireland

  - Health Care Improvement Scotland

  - Medicines and Healthcare products Regulatory Agency

  - Pfizer

  - National Clinical Guidelines Centre

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on Ivabradine for the treatment of chronic heart failure by attending the initial committee discussion and providing written evidence to the committee. They were also invited to comment on the ACD.

- Professor Martin Cowie, Professor of Cardiology, nominated by British Cardiovascular Society – clinical specialist

- Dr Suzanna Hardman, Consultant Cardiologist, Nominated by Royal College of Physicians – clinical specialist

- Dr Simon Williams, nominated by Servier Laboratories Ltd – clinical specialist

- Liz Clark, nominated by NHS Devon and Heart Care Partnership – patient expert.

The following individuals were nominated as NHS commissioning experts by the selected NHS trust allocated to this appraisal. They gave their expert/NHS commissioning personal view on ivabradine for the treatment of chronic heart failure by attending the initial committee discussion and providing written evidence to the committee. They were also invited to comment on the ACD.

- Tina Teague, Head of Locality Commissioning, selected by NHS Devon – NHS Commissioning expert.

Representatives from the following manufacturer/sponsor attended committee meetings. They contributed only when asked by the committee chair to clarify specific issues and comment on factual accuracy.

- Servier Laboratories.

ISBN: 978-1-4731-5667-8

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