Evidence Review for Surrey Cardiac Network and NHS Surrey Prescribing Clinical Network
New license indication for Ivabradine in heart failure
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1. Purpose of the Review

The European Medicines Agency has now granted a marketing licence authorisation for ivabradine for the treatment of chronic heart failure. The license states that it is suitable for patients with:

- long-term heart failure with symptoms (NYHA II to IV)
- heart failure involving systolic dysfunction
- a regular rhythm and a heart rate of 75 beats a minute or more

NICE guidance is proposed for ivabradine for the treatment of chronic heart failure in December 2012. In the interim NHS Surrey needs to consider whether it has a place in therapy in heart failure and if so whether its use should be for those patients selected using the SHIFT criteria.

Ivabradine is already licensed in the UK for long-term stable angina.

2. Appropriateness

2.1 and 2.2 The Patient and The Problem

The most common cause of heart failure in the UK is coronary artery disease (CAD). The incidence is increasing due to improved survival from conditions such as CAD and an ageing population. Patients with heart failure have a reduced quality of life and have frequent admissions to hospital. In 2009/10 in England there were just over 59,000 hospital admissions for heart failure, with a mean length of stay of 12 days. A non-elective admission to hospital in a patient with co-morbidities and complications costs £3,719.

NICE recommends ACE inhibitors and beta-blockers licensed for heart failure as first-line treatment for all patients with heart failure due to left ventricular systolic dysfunction (LVSD). Both should be started at low dosage and titrated upwards, with clinical judgement determining the choice of which drug to start first. An angiotensin-II receptor blocker (ARB) licensed for heart failure may be used as an alternative in patients intolerant of ACE inhibitors. There is a concern that general practitioners are reluctant to prescribe beta-blockers, particularly for the elderly, because of the history of adverse effects.

Various studies have shown an association between increased resting heart rate and cardiovascular (CV) and all-cause mortality. Heart rate reduction has been found to be beneficial in a range of CV conditions such as angina pectoris and heart failure. Pacemaker activity, and therefore heart rate, is influenced by ionic currents in the sinoatrial node. Ivabradine reduces heart rate by selectively antagonising this current but without affecting myocardial contractility or causing vasodilation. Ivabradine is currently licensed for the symptomatic treatment of chronic stable angina pectoris in patients with CAD and normal sinus rhythm. It is used when patients are unable to tolerate or have a contra-indication to the use of beta-blockers, or in combination with beta-blockers in patients

inadequately controlled despite an optimal beta-blocker dose if heart rate remains above 60 beats per minute (bpm).

2.3 The Intervention

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended the approval of a license extension for ivabradine to include the treatment of chronic heart failure NYHA II to IV with systolic dysfunction, in patients 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.

The CHMP adopted a new contraindication as follows:
• unstable or acute heart failure
• pacemaker dependent (heart rate imposed exclusively by the pacemaker)

How does it work

Ivabradine slows the heat rate. This may have a protective effect on the heart, and allow the heart to pump more efficiently at a slower rate.

The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

If during treatment, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. If heart rate increases persistently above 60 beats per minute at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5 mg twice daily or 5 mg twice daily.

Care setting:

The treatment has to be initiated only in patients with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic heart failure, therefore treatment would be initiated and stabilised in secondary care and continued in primary care under a shared care protocol.

2.4 Alternative treatments:
NICE recommends ACE inhibitors and beta-blockers licensed for heart failure as first-line treatment for all patients with heart failure due to left ventricular systolic dysfunction (LVSD).

There is consistent evidence that ACEI treatment improves symptoms and life expectancy in people with CHF. Treatment with an ACEI should be titrated to a target or maximum tolerated dose. Beta blockers have been shown to improve mortality and reduce hospitalisations.

Diuretics are likely to be required by most people to control congestive symptoms and fluid retention. Loop diuretics are generally preferred to thiazide diuretics.

For those patients who remain symptomatic despite optimised treatment with an ACEI, beta blocker and diuretic, specialist advice is recommended before initiating other drug treatments. Specialist treatment options include adding in an aldosterone antagonist (ie spironolactone), or adding in an A2RA (eg candesartan). There are no data from randomised controlled trails (RCTs) comparing these two approaches. Consideration should be given to the severity of symptoms and potential benefits/risks as demonstrated by the available evidence.

Digoxin is recommended as an add-on treatment for patients in sinus rhythm who remain symptomatic despite optimised treatment. However supporting evidence is limited to its use in patients receiving only ACEIs and diuretics, and there are no direct comparisons to other approaches.

In April 2012, eplerenone was licensed for use, in addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤30%). This is in addition to its existing licence for use in heart failure after a recent myocardial infarction. (In January 2012 the Prescribing Clinical Network agreed that Spironolactone should be first line with eplerenone reserved for patients with NYHA class II CHF who are intolerant to/ have contraindications to spironolactone. Eplerenone should also only be initiated under the supervision of a cardiologist and as such will be considered amber*).

3. Effectiveness

3.1 Efficacy

SHIFT was an event-driven, double-blind, placebo-controlled trial which randomised 6,558 patients with stable, symptomatic, moderate-to-severe chronic heart failure. Inclusion criteria were a hospital admission in the previous 12 months for worsening heart failure, heart rate of at least 70 bpm, left-ventricular ejection fraction (LVEF) of 35% or less and sinus rhythm.

The baseline characteristics of the allocation groups were well balanced. Patients were distributed equally between NYHA classes II and III (only 2% were in class IV). They had to be on stable and optimum background treatment for at least four weeks. Beta-blockers were up-titrated to the maximum tolerated dose. At baseline 89% of patients were taking beta-blockers, 79% ACE inhibitors and 14% ARBs. 26% of patients on beta-blockers were at target dose and 56% were prescribed at least 50% of target doses. The predominant reasons for failing to reach the target dose of beta-blocker were hypotension and fatigue. Patients were mainly white males with a mean age of 60.4 years, a mean heart rate of 79.9 bpm and a mean LVEF of 29.0%.

Patients commenced treatment with 5mg ivabradine twice daily (n=3,268) or placebo (n=3,290). After 14 days the dose was adjusted depending on heart rate and tolerability. Further adjustments could be made at study visits and mean dosage at one year was 6.5mg (standard deviation 1.6) twice daily. Median follow-up was 22.9 months (interquartile range 18 — 28).

The primary composite end point of CV death or hospital admission for worsening heart failure occurred in 793/3,241 ivabradine (24.5%) and 937/3,264 (28.7%) placebo patients;

hazard ratio (HR) 0.82 (95% confidence interval [CI] 0.75 to 0.90), P<0.0001. Hence 23 patients would require treatment over 22.9 months to prevent one CV death or one admission for heart failure. The primary end point was driven by a reduction in admissions for worsening heart failure (15.9% in the ivabradine patients vs. 20.6% placebo, P<0.0001), but CV death was not significantly different (13.9% vs. 15.0%, P=0.128). **See table below for further information**.

Heart rate was reduced in patients treated with ivabradine. A separately published analysis of SHIFT indicated that patients with the highest baseline resting heart rate had the most to gain from ivabradine. For example, in ivabradine patients with baseline heart rate of at least 87 bpm there was a decrease of 22.5 bpm at 28 days. These patients had a reduced risk of the primary composite end point: HR (adjusted for prognostic factors such as NYHA class) 0.69, 95%CI 0.58 to 0.83. For patients with baseline heart rate less than 80 bpm, the rate of the primary outcome was not statistically different. Placebo patients with high resting baseline heart rate (more than about 75 bpm) were at the highest risk of a CV event.

The authors of SHIFT highlight some limitations to the study. These include selecting patients on the basis of high baseline heart rate and being in sinus rhythm. Also, the proportion of older people in the trial was low.

A previous trial, BEAUTIFUL, studied a different population. It included 10,917 patients with CAD and LVEF of less than 40%. Patients were randomised to ivabradine or placebo with standard therapy. The primary composite end point of CV death, admission to hospital for acute myocardial infarction, and admission for new-onset or worsening heart failure was seen in 15.4% of ivabradine and 15.3% of placebo patients (P=0.94).

The results from these studies highlight that the selection of appropriate patients to receive ivabradine will be key in clinical practice.

Table: Main efficacy outcomes from the SHIFT study

	Ivabradine patients	**Placebo patients**			
Number randomised	3,268	3,290			
Number included in efficacy outcomes *	3,241	3,264			
Primary outcome			**HR (95%CI)**	**ARR**	**P value**
Composite of CV death or hospital admission for worsening heart failure	793 (24.5%)	937 (28.7%)	0.82 (0.75 to 0.90)	4.2%	<0.0001
Selected secondary outcomes					
CV death	449 (13.9%)	491 (15.0%)	0.91 (0.80 to 1.03)	1.1%	0.128
Hospital admission for worsening heart failure	514 (15.9%)	672 (20.6%)	0.74 (0.66 to 0.83)	4.7%	<0.0001

Death from heart failure	113 (3.5%)	151 (4.6%)	0.74 (0.58 to 0.94)	1.1%	0.014
* difference due to some patients not receiving treatment and two centres being removed from the trial HR Hazard ratio ARR Absolute risk reduction 95%CI 95% confidence interval					

3.2 Safety

Safety data are from the 3,232 ivabradine and 3,260 placebo patients who took at least one dose of study drug. 44.9% of ivabradine and 47.6% of placebo patients reported serious adverse events (P=0.025). Bradycardia was reported more frequently in patients on ivabradine. Symptomatic bradycardia led to withdrawal in 0.62% of ivabradine and 0.15% of placebo patients (P=0.002, number needed to harm [NNH] 212 over 22.9 months) and withdrawal due to asymptomatic bradycardia occurred in 0.87% vs. 0.15% of patients, respectively (P<0.0001, NNH 138 over 22.9 months). Visual side effects are known to occur with ivabradine and phosphenes (transient enhanced brightness) occurred in 2.75% of ivabradine and 0.52% of placebo patients (P<0.0001) in SHIFT. However withdrawals due to this were not significantly different between the groups.

The current Summary of Product Characteristics for ivabradine states that concomitant use with medicines that prolong QT is not recommended and use with potent inhibitors of CYP3A4 is contra-indicated.

3.3 Side-effects/complications

The most common side effect of ivabradine is luminous phenomena (phosphenes) which is a temporary brightness in the field of vision. Other common side effects (affecting 1 in 100 people or more) include:

Nervous system disorders:

- headaches, generally during the first month of treatment
- dizziness, possibly related to bradycardia

Eye disorders:

- blurred vision

Cardiac disorders:

- bradycardia
- AV 1st degree block (ECG prolonged PQ interval
- ventricular extrasystoles

Vascular disorders:

- uncontrolled blood pressure

3.4 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Resting heart rate below 60 beats per minute prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (< 90/50 mmHg)
- Severe hepatic insufficiency
- Sick sinus syndrome
- Sino-atrial block
- Unstable or acute heart failure
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
- Unstable angina
- AV-block of 3rd degree
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone
- Pregnancy, lactation

3.4 Place in therapy

The results of SHIFT cannot be applied to all patients with heart failure. The specific target group would encompass those patients meeting the SHIFT criteria e.g. those who have symptomatic heart failure and a LVEF of 35% or lower, are in sinus rhythm with a heart rate of at least 70 bpm, have a hospital admission for worsening heart failure within the previous 12 months and are on normal first line therapy but intolerant of high dose beta-blockers. Heart failure guidelines recommend titration of beta-blockers to target doses used in clinical trials. However, it is now clear that only some patients achieve these doses outside specialist heart failure clinics.

Ivabradine may have a place in patients who cannot take a large enough dose of beta-blocker to adequately control pulse rate. Pragmatically, ivabradine may also have a place in patients who cannot tolerate or who have a contraindication to beta-blockers. These uses do not change the first line place of beta-blockers in patients with LVSD.

4. Summary of Key Points for Consideration

4.1 Priority

To agree a Surrey wide place in therapy for Ivabradine in the treatment of chronic heart failure.

4.2 National guidance

NICE guidance is proposed for ivabradine for the treatment of chronic heart failure in December 2012.

4.3 Efficacy

In patients with moderate to severe chronic heart failure, ivabradine reduced the risk of hospitalisation for heart failure and death due to heart failure when added to standard optimum baseline treatment.

4.4 Potential Benefits
Ivabradine may be appropriate as an addition to optimal beta-blocker/ACE inhibitor therapy in patients unable to achieve sufficient heart rate reduction, or for those patients in whom beta blockers are not tolerated or are contraindicated and who still have a high pulse rate.

4.5 Potential disadvantages
The BEAUTIFUL trial found no difference between ivabradine and placebo for the primary composite end point of CV death, admission to hospital for acute myocardial infarction, and admission for new-onset or worsening heart failure; 15.4% for ivabradine and 15.3% with of placebo patients.

4.6 Budgetary Impact

The annual cost of ivabradine treatment is £522 per patient. This would be in addition to standard therapy for heart failure.

4.7 Issues for consideration
Points to consider in determining the place of ivabradine in the management of chronic heart failure:

- Only patients similar to those included in SHIFT should be considered for ivabradine. (Patients with COPD were excluded from receiving beta-blockers in the study, current NICE guidance does not consider COPD an exclusion criterion for beta-blockers, unless asthma is present).
- In patients in whom beta-blockers are not tolerated or are contraindicated and who still have a high pulse rate, then ivabradine may be a possible choice of therapy.
- In patients on an optimal dose of beta-blocker, but where the pulse rate is >70 bpm, then additional therapy should be selected from either ARBs licensed for heart failure, an aldosterone antagonist or ivabradine.
- Patients with baseline heart rate of less than 77 bpm did not benefit from ivabradine in SHIFT.
- In patients on first line therapy of beta-blocker and ACE inhibitor whose pulse rate is down adequately, but who are still symptomatic then consider treatments other than ivabradine.
- Unlike beta-blockers, ivabradine did not have a significant effect on CV or all-cause mortality. However, the trial was not powered to show a mortality benefit.
- Use in patients with NYHA class IV remains unproven (only 2% or patients in the trial had heart failure NYHA class IV).
- Further trials would be necessary to test ivabradine in patients who would not meet the SHIFT criteria.

5. Conclusions and Recommendations

Ivabradine is now indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients 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.

NICE guidance is proposed for ivabradine for the treatment of chronic heart failure in December 2012. In the interim NHS Surrey needs to consider whether it has a place in

therapy in heart failure and if so, whether its use should be for those patients selected using the SHIFT criteria.

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