Scottish Medicines Consortium
Providing advice about the status
of all newly licensed medicines

www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP   Tel 0141 225 6999   Chairman: **Professor Angela Timoney** FRPharmS

NHS
SCOTLAND

ivabradine 5 and 7.5mg film-coated tablets (Procoralan®)
SMC No. (805/12)
Servier Laboratories Ltd

07 September 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

ivabradine (Procoralan®) is accepted for restricted use within NHS Scotland.

Indication under review: Chronic heart failure New York Heart Association (NYHA) II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥75 beats per minute (bpm), in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contra-indicated or not tolerated.

SMC restriction: for initiation only in patients whose resting heart rate remains ≥75 beats per minute despite optimal standard therapy.

In a post-hoc subgroup analysis of the pivotal study in patients meeting the licensed indication, ivabradine was significantly more effective than placebo at reducing the risk of a composite of cardiovascular death or hospitalisation for worsening heart failure. However, in patients on the target dose of beta-blocker, ivabradine was not significantly more effective.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 08 October 2012

Indication

Chronic heart failure New York Heart Association (NYHA) II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 beats per minute (bpm), in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contra-indicated or not tolerated.

Dosing Information

The usual recommended starting dose of ivabradine is 5mg twice daily. After two weeks of treatment, the dose can be increased to 7.5mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5mg twice daily (one half 5mg 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 5mg twice daily should be maintained.

If during treatment, heart rate decreases persistently below 50 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 7.5mg twice daily or 5mg twice daily. If heart rate increases persistently above 60 bpm at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5mg twice daily or 5mg twice daily. Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist.

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.

Product availability date

February 2012

Summary of evidence on comparative efficacy

Ivabradine is the first specific inhibitor of the cardiac pacemaker I_f current to be licensed for the treatment of heart failure. It acts to slow heart rate by selectively and specifically inhibiting the I_f current that controls spontaneous diastolic depolarisation in the sinus node. Ivabradine has been accepted for restricted use within NHS Scotland for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm for whom heart rate control is desirable and who have a contra-indication or intolerance to beta-blockers and rate-limiting calcium-channel blockers. Ivabradine is also licensed for the symptomatic treatment of chronic stable angina pectoris in adults with coronary artery disease with normal sinus rhythm in combination with beta-blockers when inadequately controlled with an optimal dose and whose heart rate is ≥60 bpm. However, in the absence of a submission from the holder of the marketing authorisation, SMC issued advice that ivabradine was not recommended for use within NHS Scotland. The indication currently under review is for patients with chronic heart failure NYHA 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 contra-indicated or not tolerated.

The evidence to support this indication comes from a large, phase III, placebo-controlled, randomised, clinical study (SHIFT)[1,2,3], which recruited 6,505 adult patients with chronic heart

failure NYHA class II to IV that had been stable for at least 4 weeks. Eligible patients were in sinus rhythm, had a left ventricular ejection fraction (LVEF) ≤35% and a resting heart rate ≥70 bpm, and had a previous admission to hospital for worsening heart failure within the preceding 12 months. Patients were required to be on optimal stable background treatment for heart failure for at least 4 weeks prior to inclusion.

Following a two week run-in period, eligible patients were randomised to receive ivabradine or placebo in addition to their continued therapy for heart failure, including beta-blockade. Randomisation was stratified by centre and by whether or not receiving beta-blocker treatment at baseline. Ivabradine was initiated at a dose of 5mg twice daily and increased after two weeks to 7.5mg twice daily, unless the resting heart rate was ≤60bpm; if heart rate was 50 to 60bpm, the ivabradine dose remained at 5mg twice daily; if heart rate was <50bpm or the patient had signs or symptoms of bradycardia, the ivabradine dose was reduced to 2.5mg twice daily. Doses were adjusted in this manner at follow-up visits at 1 month, 4 months and then every 4 months thereafter. The two treatment groups were well matched. In the total study population (heart rate ≥70 bpm, n=6,505), the mean age was 60 years; 76% were male; 68% had ischaemic causes of heart failure; 49% had NYHA class II, 50% had class III and 1.7% had class IV; mean heart rate was 80 bpm, mean systolic and diastolic blood pressures were 122 and 76mm Hg and mean LVEF was 29%. At baseline, patients were receiving the following treatments: beta-blockers (89%), angiotensin converting enzyme (ACE) inhibitors (79%), angiotensin receptor blockers (ARBs) (14%), diuretics (83%), aldosterone antagonists (60%) and cardiac glycosides (22%). In terms of beta-blocker therapy, 23% (1,488/6,505) of all study patients were considered to be on a target dose and 49% (3,181/6,505) were on at least half the target dose.

The primary outcome was a composite of cardiovascular death or hospital admission for worsening heart failure. All deaths were considered to be cardiovascular unless there was an established non-cardiovascular cause. In the total study population, after a median follow-up of 22.9 months, the composite primary endpoint was reported in 24% (793/3,241) ivabradine and 29% (937/3,264) placebo patients, corresponding to a hazard ratio (HR) of 0.82 (95% confidence interval [CI]: 0.75 to 0.90), p<0.0001. This equates to an 18% relative risk reduction and a 4.2% absolute risk reduction. The difference between the treatment groups was mainly driven by fewer hospitalisations for worsening heart failure in the ivabradine compared with the placebo group: (16% [514/3,241] versus 21% [672/3,264] respectively, HR 0.74 [95% CI: 0.66 to 0.83], p<0.0001). There was no significant difference between the groups in cardiovascular death (14% [449/3,241] versus 15% [491/3,264] respectively; HR 0.91 [95% CI: 0.80 to 1.03], p=0.128).

A post-hoc subgroup analysis assessed the treatment effect in the proportion of patients with a heart rate ≥75 bpm.[3,4] This subgroup comprised 64% (4,150/6,505) of the total SHIFT study population and represents the licensed population. These patients had a mean age of 60 years; 77% were male; 66% had ischaemic causes of heart failure; 47% had NYHA class II, 51% had class III and 2.1% had class IV; mean heart rate was 84.5 bpm, mean systolic and diastolic blood pressures were 121 and 76mm Hg and mean LVEF was 28.7% and 28.5%. At baseline patients were receiving the following treatments: beta-blockers (88%), ACE inhibitors and/or ARBs (90%), diuretics (84%), aldosterone antagonists (62%) and cardiac glycosides (24%). In terms of beta-blocker therapy, 23% (938/4,150) of patients in the licensed subgroup were considered to be on a target dose and 48% (1,986/4,150) were on at least half the target dose. In this subgroup, after a median follow-up of 22.5 months, the composite primary outcome was reported in 27% (545/2,052) ivabradine and 33% (688/2,098) placebo patients, corresponding to

a HR of 0.76 (95% CI: 0.68 to 0.85), p<0.0001. This equates to a 24% relative risk reduction and a 6.2% absolute risk reduction. The difference between the treatment groups was mainly driven by fewer hospitalisations for worsening heart failure in the ivabradine compared with the placebo group (18% [363/2,052] versus 24% [503/2,098] respectively; HR 0.70 [95% CI: 0.61 to 0.80], p<0.0001). However, the difference between the groups in cardiovascular death also reached statistical significance (15% [304/2,052] versus 17% [364/2,098] respectively; HR 0.83 [95% CI: 0.71 to 0.97], p=0.017).

Key secondary outcomes included all cause mortality, which was not significantly different between ivabradine and placebo in the total population (16% [503/3,241] and 17% [552/3,264] respectively; HR 0.90 [95% CI: 0.80 to 1.02], p=0.092), but was in the licensed subgroup (17% [340/2,052] and 19% [407/2,098] respectively; HR 0.83 [95% CI: 0.72 to 0.96], p=0.011). Death from heart failure was significantly reduced by ivabradine in both populations: 3.5% (113/3,241) ivabradine and 4.6% (151/3,264) placebo patients; HR 0.74 (95% CI: 0.58 to 0.94), p=0.014 in the total population and 3.8% (78/2,052) ivabradine and 6.0% (126/2,098) placebo patients; HR 0.61 (95% CI: 0.46 to 0.81), p=0.0006 in the licensed subgroup.

Quality of life assessment using the disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ) was completed by a subgroup of the SHIFT study: there were statistically but not clinically significant improvements with ivabradine compared with placebo at 12 months in the KCCQ clinical summary score and the KCCQ overall summary score.[5]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The safety profile of ivabradine in patients with heart failure was consistent with previous studies. The frequency of adverse events appeared to be similar in the total study population and the subgroup that formed the licensed population. In the licensed population, the most frequently reported adverse events in the ivabradine and placebo groups were atrial fibrillation (7.9% and 6.8% respectively), asymptomatic bradycardia (4.8% and 1.2% respectively), symptomatic bradycardia (4.1% and 0.7% respectively), visual disturbances (phosphenes [2.8% and 0.5% respectively] and blurred vision [0.5% and 0.3% respectively]).[1,3,4]

Summary of clinical effectiveness issues

Ivabradine is the first specific inhibitor of the cardiac pacemaker I_f current to be licensed for the treatment of heart failure. In the pivotal, phase III, SHIFT study, ivabradine, in addition to standard optimal therapy, reduced the composite risk of cardiovascular death and hospitalisation due to worsening heart failure in patients with heart failure (NYHA class II to IV) and low ejection fraction who were in sinus rhythm and had a resting heart rate ≥70 bpm. The evidence for the licensed population (heart rate ≥75 bpm) comes from a post-hoc subgroup analysis in 64% of the overall study population and so results should be interpreted with care since the subgroup was not predefined, may not be balanced by the randomisation and may not be powered. The reduction in the composite endpoint was driven by a significant reduction in hospital admission for worsening heart failure and there was no significant difference between ivabradine and placebo in terms of cardiovascular death in the total population.[5,8] However, in the licensed population, the difference between ivabradine and placebo did reach statistical

significance for cardiovascular death. Death from any cause was reported as a secondary outcome and was significantly reduced in the ivabradine group in the licensed population only.

During the study, both treatment groups received concomitant therapy with current, guideline-based therapy with particular attention to beta-blockade. However, only 23% (1,488/6,505) of patients received the target doses and 49% (3,181/6,505) at least half of target doses of beta-blockers. The authors of the key publication note that the doses of beta-blockers used were lower than those used in clinical outcome studies of beta-blockers but believe they more closely mirror clinical practice and are higher than doses reported in surveys.[5] Subgroup analyses in the total and licensed populations suggest that at higher beta-blocker doses the treatment benefits of ivabradine are reduced and do not reach statistical significance. The summary of product characteristics (SPC) notes that in the subgroup of patients who received the target dose of beta-blocker from the licensed population, there was no statistically significant difference for the primary composite endpoint, hospitalisation for worsening heart failure or death from heart failure.

Patients enrolled in the SHIFT study had a mean age of 60 years which is younger than would be expected for heart failure patients in Scotland. However, additional subgroup analyses of treatment effects for patients aged ≥65 years and ≥70 years found similar results to the total study population.[3] Mean blood pressure at baseline in the SHIFT study was 122/76mm Hg and the European Medicines Agency (EMA) commented that this was lower than in other studies and clinical practice surveys. This was cited as the main reason for failure to reach target beta-blocker dose.[3] Only a small proportion of patients in the SHIFT study had NYHA class IV disease (1-2%) and the SPC notes that ivabradine should be used with caution in these patients due to the limited amount of data.

Ivabradine provides another treatment option to slow heart rate in patients with heart failure. However, beta-blockers have demonstrated consistent survival benefit in patients with heart failure and ivabradine should not be considered an alternative to them. SMC clinical experts have advised that the treatment priority in heart failure is to maximise the use of ACE inhibitors (or an angiotensin II receptor blocker) plus a beta-blocker and an aldosterone antagonist at evidence-based doses. They advised that the benefits of ivabradine are less certain and its use in addition to standard therapy should be considered only in patients with resting heart rate ≥75 bpm despite optimal background therapy including beta-blockade or as an alternative to slow heart rate in patients with absolute contra-indications or intolerance of beta-blockers.

Summary of comparative health economic evidence

The submitting company presented a lifetime cost-utility analysis comparing ivabradine in addition to standard care with standard care alone in the licensed population of patients with chronic heart failure NYHA class II to IV who are in sinus rhythm and whose heart rate is ≥75 bpm. Standard care included guideline-based therapies and was estimated on the proportion of patients receiving each treatment in the SHIFT study. For the majority of patients this included a beta-blocker and an ACE inhibitor.

A Markov cohort model was used which captured information relating to mortality, hospitalisations, quality of life and NYHA functional class. The model used risk equations estimated from the whole trial population of the SHIFT study, which differed from the patient group specified in the licence. The submitting company argued this approach can be

considered conservative as the hazard ratios based on the whole trial population were less favourable for ivabradine. Patients who remained alive in the model were distributed according to NYHA class in order to capture differences in quality of life associated with the different stages of heart failure, with more patients in the ivabradine arm distributed into milder NYHA classes. In order to extrapolate the trial data over the duration of the model a parametric survival model was used, with the Gompertz model selected as the best fit to the data. The treatment effect of ivabradine plus standard care was assumed to continue beyond the trial period until the patient dies.

Quality of life data were collected in the SHIFT study where EQ-5D was completed at baseline, 4, 12, 24 and 36 months. EQ-5D scores were then converted to utility values using UK population tariff scores to give utility values according to NYHA functional class, with utility decrements applied due to hospitalisations. The rate of hospitalisation was collected in the trial and was assumed to occur at a constant rate. Disease management costs, such as physician visits, outpatient procedures and diagnostic tests were also included.

The company estimated an incremental cost-effectiveness ratio (ICER) of £6,002 per quality-adjusted life-year (QALY) based on an incremental cost of £1,875 and a QALY gain of 0.31. A scenario analysis was provided where the baseline characteristics were adjusted to better reflect the Scottish heart failure population. The ICER for this analysis was estimated to be £5,310 based on an incremental cost of £1,389 and a QALY gain of 0.26.

The following issues were noted:
- The co-primary endpoint of reduction in cardiovascular death did not reach significance in the whole population but the numerical difference was used in the economic model. The results were sensitive to changes in this parameter with the cost per QALY increasing to £14k when the upper 95% confidence interval was used. However, it should be noted that in this sensitivity analysis the upper 95% confidence interval exceeds 1 implying that ivabradine is less effective than standard care alone.
- The inclusion of a utility gain associated with ivabradine treatment in addition to patients in this arm being in better NYHA health states may have introduced a bias in favour of ivabradine. A sensitivity analysis was provided where this additional utility gain was removed and this resulted in the ICER increasing to £7,251 per QALY.
- The treatment effect of ivabradine plus standard care was assumed to continue beyond the trial period until the patient dies with no reduction in treatment effect over time. Sensitivity analysis was provided where the treatment effect tailed off over 5 years and this resulted in the cost per QALY increasing to £9k.

Despite these issues, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

European Society of Cardiology (ESC) published "Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012". This guideline recommends the following in potentially all

patients with systolic heart failure to reduce the risk of heart failure hospitalisation and the risk of premature death:

- an ACE inhibitor (or if not tolerated, an ARB] in addition to a beta-blocker, for all patients with symptomatic heart failure (NYHA II to IV) and an ejection fraction ≤40%.
- a beta-blocker in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated) for all patients with symptomatic heart failure (NYHA II to IV) and an ejection fraction ≤40% .
- a mineralocorticoid receptor antagonist (spironolactone or eplerenone) for all patients with persisting symptoms (NYHA II to IV) and an ejection fraction ≤35%, despite treatment with an ACE inhibitor or ARB if ACE inhibitor not tolerated) and a beta-blocker.

The guideline also notes a number of other treatments with less certain benefits in patients with symptomatic NYHA II to IV systolic heart failure. The guidance states that ivabradine should be considered:

- in patients in sinus rhythm with an ejection fraction ≤35%, a heart rate remaining ≥70bpm (approved for use in patients with a heart rate ≥75bpm) and persisting symptoms despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or an ARB).
- in patients in sinus rhythm with an ejection fraction ≤35%, a heart rate remaining ≥70bpm (approved for use in patients with a heart rate ≥75bpm) who are unable to tolerate a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or an ARB).

Ivabradine may be considered in patients with a contra-indication to a beta-blocker or beta-blocker intolerance.

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline (CG) 108 "Chronic Heart Failure" in August 2010. This guideline recommends that both ACE inhibitors and beta-blockers licensed for heart failure should be offered to all patients with heart failure due to left ventricular systolic dysfunction. Specialist advice should be sought before offering second-line treatment to patients with heart failure due to left ventricular systolic dysfunction. Consider adding one of the following if a patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker:

- an aldosterone antagonist licensed for heart failure (especially if the patient has moderate to severe heart failure [NYHA class III–IV] or has had a myocardial infarction [MI] within the past month) or
- an ARB licensed for heart failure (especially if the patient has mild to moderate heart failure [NYHA class II–III]) or
- hydralazine in combination with nitrate (especially if the patient is of African or Caribbean origin18 and has moderate to severe heart failure [NYHA class III–IV]).

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 95 "Management of Chronic Heart Failure" in February 2007. This guideline recommends that ACE inhibitors should be considered in patients with all NYHA functional classes of heart failure due to left ventricular systolic dysfunction and that beta-blocker therapy should be started as soon as their condition is stable in these patients (unless contraindicated by a history of asthma, heart block or symptomatic hypotension). Patients with chronic heart failure due to left ventricular systolic dysfunction alone, or heart failure, left ventricular systolic dysfunction or both following MI who are intolerant of ACE inhibitors should be considered for an angiotensin receptor blocker. Patients with heart failure due to left ventricular systolic dysfunction who are still symptomatic despite therapy with an ACE inhibitor and a beta blocker may benefit from the addition of candesartan, following specialist advice. Also, following specialist advice, patients

with moderate to severe heart failure due to left ventricular systolic dysfunction should be considered for spironolactone unless contraindicated by the presence of renal impairment or a high potassium concentration. In patients who develop gynaecomastia, eplerenone can be substituted for spironolactone. Patients who have suffered a MI and with left ventricular ejection fraction ≤40% and either diabetes or clinical signs of heart failure should be considered for eplerenone unless contraindicated by the presence of renal impairment or a high potassium concentration. The SIGN website indicates that a review of this guideline is being considered.

Additional information: comparators

Other treatment options available for patients who are not controlled on standard therapy (beta-blocker, ACE inhibitor alone) include eplerenone, spironolactone, candesartan and digoxin. There are no direct comparators with ivabradine.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
ivabradine	**5 to 7.5mg twice daily**	**522**
eplerenone	25 to 50mg once daily	555
candesartan	4 to 32mg once daily	25 to 52
spironolactone	25 to 50mg once daily	20 to 31

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 18 June 2012. Note: there are differences between these medicines in the specific licensed indication for heart failure.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 4680 in year 1 rising to 8,388 in year 5 with an estimated uptake rate of 10% in year 1 and 50% in year 5. The gross impact on the medicines budget was estimated to be £214k in year 1 and £1.92m in year 5. As no other drugs were assumed to be displaced, the net medicines budget impact remains the same at £214k in year 1 and £1.92m in year 5. SMC clinical experts suggest that these patient numbers may be an overestimate.

References

The undernoted references were supplied with the submission.

1. Swedberg K, Komadja M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. The Lancet 2010;376(9744):875-85.

2. Swedberg K, Komadja M, Bohm M, et al. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart failure treatment with I_f inhibitor Ivabradine Trial (SHIFT). European Journal of Heart Failure 2010;12:75-81.

3. European Medicines Agency European Public Assessment Report (EPAR).for Procoralan® EMEA/H/C/000597/II/0018 www.ema.europa.eu [accessed 7 June 2012]

4. Bohm M, Borer J, Ford I et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. Clin Res Cardiol 2012; doi 10.1007/s00392-012-0467-8

5 .Swedberg K, Komajda M, Bohm M et al. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta blocker dose? Findings from the SHIFT-study. Journal of the American College of Cardiology 2012;59(22):1938-45.

6. Ekman I, Chassany O, Komajda M, Bohm M, Borer J, Ford I, et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. European Heart Journal 2011;32:2395-404.

This assessment is based on data submitted by the applicant company up to and including **17 August 2012.**

Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.   SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.