Scottish Medicines Consortium

ivabradine 5mg, 7.5mg tablets (Procoralan) No. (319/06)

Servier Laboratories Limited

9 February 2007

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

ivabradine (Procoralan®) is 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 for beta-blockers and rate-limiting calcium-channel blockers.

Non-inferiority of ivabradine versus a beta blocker and a calcium-channel blocker was shown in two controlled trials. Long-term protection against cardiovascular events, however, has not been demonstrated.

Overleaf is the detailed advice on this product.

Vice-Chairman,
Scottish Medicines Consortium

Indication

Symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contra-indication or intolerance for beta-blockers.

Dosing information

Starting dose; 5mg twice daily. After three to four weeks of treatment the dose may be increased to 7.5mg twice daily depending on therapeutic response.

Product availability date

October 2005

Summary of evidence on comparative efficacy

The I_f current is one of several ionic currents responsible for influencing spontaneous depolarisation of the sinoatrial (SA) node. Ivabradine is a selective sinus node I_f inhibitor which slows the diastolic depolarisation slope of the SA-node resulting in a reduction in heart rate.

Two phase III randomised, double-blind, active comparator studies, powered for non-inferiority, have been conducted. Patients were included if they were aged 18-75 years, with a history of chronic effort angina for at least 3 months, no angina at rest, no significant change in frequency, severity or triggering activity within 1 month preceding inclusion and no change in nitrate consumption at the end of the run-in period. Patients were required to have a qualifying exercise tolerance test (ETT) that met positivity and stability criteria at selection and at the end of a run-in period.

In both studies the primary endpoint was the change in total exercise duration (TED) measured in seconds using a treadmill or bicycle ETT performed at trough of drug activity. Secondary endpoints included time to limiting angina (TLA), time to onset of angina (TAO), and time to 1 mm ST segment depression (TST) measured during the ETT. Reasons for terminating exercise were limiting angina, dyspnoea or extreme fatigue.

In the first study the main analysis of outcomes was performed on the full analysis set (all randomised patients with documentation of coronary artery disease having taken at least one dose of study medication and who had an evaluation of the primary efficacy criterion during the randomised therapy period). Patients were randomised to receive either ivabradine 5mg twice daily or atenolol 50mg once daily for 4 weeks. This was followed by three months treatment at doses of ivabradine 7.5mg twice daily (n=300) or 10mg twice daily (n=298), randomly assigned, or atenolol 100mg once daily (n=286). A non-inferiority margin of 35 seconds was applied. Baseline TED values for the ivabradine 7.5mg, and atenolol groups were 595 and 578 seconds and the change from baseline at the end of the study was 87 and 79 seconds respectively. Non-inferiority of ivabradine compared to atenolol was shown.

Non-inferiority was also shown for TLA, TAO and TST. A secondary analysis showed non-inferiority between the ivabradine 5mg twice daily and the atenolol 50mg once daily groups (at 4 weeks) for the primary and secondary efficacy variables detailed.

In the second study patients were randomised to receive ivabradine 7.5mg twice daily (n=400), 10mg twice daily (n=391) or amlodipine 10mg once daily (n=404) for 3 months. A non-inferiority margin of 30 seconds was applied. For the primary efficacy endpoint, TED, the change from baseline was 28 and 31 seconds for the ivabradine 7.5mg and amlodipine

groups respectively. Non-inferiority of ivabradine compared with amlodipine was established. Similar results were also shown for TLA, TAO and TST.

Long-term efficacy of ivabradine was assessed in three 1-year safety studies. In the first study 318 patients with stable effort angina were randomised to either ivabradine 10mg twice daily or atenolol 100mg once daily. The second study recruited 386 patients who were treated with either ivabradine 5mg twice daily or 7.5mg twice daily. The third study (n=660) was an open label extension study where patients received ivabradine 7.5mg twice daily. In all studies the principal efficacy criterion (defined as a secondary objective) was the mean number of angina attacks per week and the mean consumption of short-acting nitrates per week based on patients' diary records.

In the first and second long-term studies there were sustained significant reductions in angina attack frequency and short-acting nitrate consumption in patients treated with ivabradine over the 1-year study periods.

Summary of evidence on comparative safety

Adverse effects observed in patients taking ivabradine 5mg and 7.5mg twice daily in the combined safety data set presented to the European Medicines Agency (EMEA) and reported by at least 0.1% of patients included phosphene-like events (transient enhanced brightness in a limited area of the visual field) (14.5%). An analysis of visual disturbances in a subset of 2545 patients treated with ivabradine was included in the submission to the EMEA. The incidence of visual disturbances was higher in the ivabradine group (17%) compared to all other groups (3-7%) and appeared to be dose related (ivabradine 5mg;14% and ivabradine 7.5mg 18%). The majority of disturbances were phosphene-like events which were mild to moderate, resolved during treatment, and their impact on patients' daily life was low.

The scientific discussion of the European Public Assessment Report (EPAR) details emergent eye and cardiac adverse events reported by at least 0.5% of patients in the overall oral safety set (which includes all studies except follow-up periods). Eye disorders were reported in 17%, 9.6% and 4.7% of patients on ivabradine (5mg or 7.5mg doses), atenolol and amlodipine and cardiac disorders were reported in 18%, 15% and 13% of patients respectively.

Summary of clinical effectiveness issues

The manufacturer's submission proposes that ivabradine be recommended for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contra-indication or intolerance for beta-blockers and calcium channel blockers. This represents a sub-group within the licensed indication and there are no clinical data specific to this sub-group.

Concomitant treatment with drugs that could interfere with the natural course of angina (e.g. long-acting nitrates, calcium antagonists) or interpretation of the ST-segment changes (e.g. anti-arrhythmic agents, digoxin) was not allowed during the controlled trials. In addition, treatment was not limited to patients unable to use beta-adrenoceptor blocking drugs (and indeed any contra-indication to atenolol was a specific exclusion criterion in the active comparator study using atenolol). Therefore it is possible that the trial populations are not representative of the Scottish population that would be eligible for ivabradine.

Although in the second trial non-inferiority of ivabradine versus amlodipine was statistically demonstrated at the pre-defined non-inferiority margin of 30 seconds (s), the robustness of this result was questioned by the EMEA, when the effect sizes of 28s for ivabradine 7.5mg and 31s for amlodipine are considered. The estimated between group difference is 1.8s (95% CI -14.6, 11.6). The predefined non-inferiority margin of 30s was considered too lenient and the obtained lower limit did not sufficiently rule out inferiority. However, a post hoc analysis confirmed the non-inferiority of ivabradine 7.5mg twice daily to amlodipine, using a margin of 15s.

The effect of ivabradine on morbidity and mortality in cardiovascular disease has not been determined, as the clinical trials were not large enough for this assessment and it is not a requirement of the EMEA licensing procedure. An ongoing trial, due to report in 2009, has a primary objective of demonstrating the superiority of ivabradine over placebo in the reduction of cardiovascular mortality and hospital admissions for acute myocardial infarction and/or new onset or worsening heart failure.

Summary of comparative health economic evidence

A simple cost-utility analysis was submitted for ivabradine 7.5mg twice daily compared to no treatment for symptom relief in patients with chronic stable angina who are contraindicated or intolerant to beta-blockers and calcium channel blockers. However, this comparator may not be appropriate, and no evidence was presented compared to other possible treatment options currently available in Scotland such as long acting nitrates or the potassium channel activator, nicorandil.

For the comparison with no treatment, SF36 data obtained from the ivabradine 7.5mg arm of a phase III trial of ivabradine v atenolol (a beta-blocker) was converted into utilities, and the change in utility from baseline to month 4 follow up was used to estimate the annual QoL benefit of symptom relief associated with ivabradine. The utility gain for the ivabradine patients was validated by reference to a similar utility outcome for patients receiving atenolol in the comparator arm of the trial. Costs included were the cost of ivabradine for a year and a single GP visit. The justification for primary care resource use estimates were not provided and costs of managing ivabradine related adverse events were not estimated. The base case result was an estimated incremental cost per QALY gained for ivabradine v no treatment of £15,021 and a range of £9,737 to £32,638 based on the 95% confidence intervals for the change from baseline in utility outcomes. No other sensitivity analysis was conducted (for example on resource use estimates). However, the main driver of cost-effectiveness was the utility outcome.

There are concerns over the comparator chosen and uncertainty concerning the cost-effectiveness of ivabradine compared to no treatment, but there may be a small group of patients with no other treatment options in whom ivabradine may be appropriate.

Summary of patient and public involvement

Patient Interest Group Submission: British Cardiac Patients Association

Additional information: guidelines and protocols

The Scottish Intercollegiate Guideline Network (SIGN) guideline on the management of stable angina was published in February 2007. It continues to recommend beta-blockers as first-line therapy and adds that rate-limiting calcium channel blockers, long-acting nitrates or nicorandil are options for patients intolerant to beta-blockers. Ivabradine is not included in any recommendation. The guideline comments that it was shown to have equivalent anti-anginal efficacy to atenolol in patients with stable angina but adds, "While symptomatic benefit has been clearly demonstrated long term protection against cardiovascular events has yet to be determined."

The European Society of Cardiology's guideline on the management of stable angina pectoris was published in 2006. They recommend either a calcium channel blocker or long-acting nitrate, potassium channel activator or If inhibitor in patients who are intolerant or have a contraindication to a beta blocker or whose symptoms are not controlled by them.

Additional information: previous SMC advice

In September 2006, following a full submission, the Scottish Medicines Consortium advised that ivabradine is not recommended for use within NHS Scotland for the symptomatic treatment of chronic stable angina in patients with normal sinus rhythm who have a contra-indication or intolerance for beta-blockers.

Non-inferiority of ivabradine versus a beta blocker and a calcium-channel blocker was shown in two controlled trials however the economic case for ivabradine has not been demonstrated.

Additional information: comparators

Calcium-channel blockers, nitrates and potassium-channel activators are alternatives when beta-blockers are contra-indicated or not tolerated.

Additional information: costs

The following selection illustrates a range of preparations licensed in the treatment of angina pectoris but is by no means exhaustive.

Doses are shown for general comparison and do not imply therapeutic equivalence.

Drug	Usual daily dose range	Cost *per year (£)
ivabradine	**10-15mg**	**507**
Calcium channel blockers		
amlodipine	5-10mg	28-34
nifedipine twice daily (MR)	20-80mg	52-194
verapamil long acting (e.g Securon SR)	240-480mg	76-153
felodipine (Felogen XL)	5-10mg	89-156
diltiazem long acting (e.g Adizem-XL)	240-300mg	126-158
nifedipine once daily (e.g. Coracten XL)	30-90mg	77-191
nicardipine	60-120mg	120-240
nisoldipine	20-40mg	228-456
Potassium channel activator		
nicorandil	20-40mg	99-189
Nitrate		
isosorbide mononitrate standard release	80-120mg	31-46
isosorbide mononitrate long acting (e.g. Imdur)	60-120mg	145-290

*costs from eVadis drug dictionary accessed on November 2006.

Additional information: budget impact

The manufacturer estimated the net budget impact of ivabradine at £232k in 2007, based on an average duration of 6 months treatment in the first year, rising to a full year cost of £942k in 2008 and £1.9M in 2011. The estimate assumed 879 patients would receive ivabradine in 2007, based on use in 5% of patients who currently receive prophylactic nitrates or nicorandil, rising to 20% uptake in 2011. The budget impact is likely to be considerably smaller as SMC has restricted the use of the product to patients in whom beta-blockers and calcium channel blockers are contra-indicated or not tolerated.

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.

This assessment is based on data submitted by the applicant company up to and including 12 January 2007.

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.

The undernoted reference was supplied with the submission.

Tardif J-C, Ford, I., Tendera M.,et al, for the INITIATIVE Investigators. Efficacy of ivabradine, a new selective I_f inhibitor, compared with atenolol in patients with chronic stable angina. European Heart Journal. 2005; 26: 2529–2536