PUBLIC SUMMARY DOCUMENT
Product: Ivabradine hydrochloride, film coated tablets, 5 mg and 7.5 mg, Coralan®
Sponsor: Servier Laboratories (Australia) Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application

This second submission sought an Authority required PBS listing for the treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients contraindicated or intolerant to beta blockers and with a heart rate of 75 beats per minute or greater.

2. Background

At the November 2007 meeting, the PBAC rejected a first submission for ivabradine for an Authority required listing for chronic stable angina due to artherosclerotic coronary artery disease because of difficulty in interpreting the clinical comparison with diltiazem and, critically, because of insufficient evidence to support the claim that ivabradine's superiority over diltiazem and/or amlodipine in terms of heart rate reduction, translates into reduced cardiovascular mortality, thus providing an insufficient basis to support the cost-effectiveness analysis. *(See PBAC Public Summary Document – November 2007)*

3. Registration Status

Ivabradine was TGA registered on 27 October 2006 for the treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm who are unable to tolerate or have a contraindication to the use of beta blockers.

4. Listing Requested and PBAC's View

Authority Required

Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm who are unable to tolerate or who have a contraindication to the use of beta blockers and have a resting heart rate of 75 bpm or greater.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Ivabradine would provide an alternative option for the treatment of chronic stable angina, due to atherosclerotic artery disease in patients with normal sinus rhythm, who are unable to tolerate or have a contra-indication to the use of beta-blockers and have a resting heart rate of 75bpm or greater.

6. Comparator

The submission nominated diltiazem as the main comparator and amlodipine as the secondary comparator.

Although the PBAC agreed that diltiazem and amlodipine are reasonable comparators, the PBAC reiterated its view that a comparison with the long acting nitrates was also appropriate.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

No changes were made to the ivabradine trial data presented in the November 2007

submission. However, one indirect comparison was re-performed and new diltiazem meta-analysis data were presented in this submission.

The submission presented the following trials:

- 10 randomised trials indirectly comparing ivabradine (7.5mg/5mg twice daily) and diltiazem (180mg to 360mg daily) using either amlodipine (3 trials) or placebo (7 trials) as the common reference.
- One direct randomised trial (CL3-023) comparing ivabradine (7.5mg twice daily) to the minor comparator, amlodipine (10mg once daily).

The trials published at the time of submission are as follows:

Trial ID-Phase/ First author	Protocol title/ Publication title	Publication citation
Indirect comparison: common reference of placebo		
Ivabradine		
CL2-009-Phase II [a] Fox, K.	Ivabradine: a selective and specific I_f inhibitor: efficacy and safety in stable angina	Eur Heart J 2003; 5(suppl):G36-G45
Borer, J.S., et al	Antianginal and antiischemic effects of ivabradine, an I_f inhibitor, in stable angina: a randomised, double-blind, multicentered, placebo-controlled trial	Circulation 2003;107(6):817-823
Diltiazem		
Go, M.,et al	Improved efficacy of high-dose versus medium- and low-dose diltiazem therapy for chronic stable angina pectoris	Am J Cardiol, 1984; 53:669-73
Hossack, K.F., et al	Long-term study of high-dose diltiazem in chronic stable exertional angina	Am Heart J,1984; Vol 107:1215
Khurmi, N.S., et al	Long-term efficacy of diltiazem assessed with multistage graded exercise tests in patients with chronic stable angina pectoris.	Am J Cardiol, 1984; 54:738-743
Maranhao, M.F.C., [b] et al	Translated title: Myocardial ischemia with stable angina pectoris:clinical ergometric evaluation with diltiazem	Arq Bras Cardiol, 1992; 58(2):149-55
Strauss, W.E., et al	Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: report of a cooperative clinical trial.	Am J Cardiol, 1982; 49:560-66
Weiner, D.A., et al	Efficacy and safety of sustained-release diltiazem in stable angina pectoris.	Am J Cardiol, 1986; 57:6-9
Indirect comparison: common reference of amlodipine		
Diltiazem		
Chugh, S.K., et al	A randomised, double-Blind comparison of the efficacy and tolerability of once-daily modified-release Diltiazem Capsules with once-daily amlodipine tablets in patients with stable angina.	J Card Pharm, 2001; 38:356-64
Merchand, X., et al	Translated from French: Evaluation of amlodipine in stable effort angina. Comparison with diltiazem in terms of efficacy, safety and maintenance of the anti-ischemic action 24 hours after last dose.	Ann de Cardiol et D'Angeiol, 1996; 45(2):74-82
Ivabradine		
CL3-023-Phase III Ruzyllo, W., et al	Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: A 3-month randomised, double-blind, multi-centre, non-	Drugs, 2007;67(3):393-405

	inferiority trial.	
Direct comparison: ivabradine versus the minor comparator, amlodipine		
CL3-023- Phase III	As above	As above

[a] consists of two main sub-studies: a dose ranging double blind randomised placebo controlled trial (2 weeks in duration: also called P1-P2 period) followed by a "two or three month" (as defined in the clinical study report: CL2-009) open-label safety study of 10mg ivabradine and a one-week run-out phase period (P3 period); [b] foreign language with only abstract available in English; S16257 = ivabradine; I_f = funny current.

8. Results of Trials

The results of the indirect comparison of ivabradine and diltiazem were expressed in terms of heart-rate reduction effect.

The results of the comparisons of heart-rate reduction are summarised in the table below:

Summary of Indirect Comparisons of Ivabradine and Diltiazem – Incremental difference in Heart Rate Lowering Effects, at various doses.

	Diltiazem 240mg d	**Diltiazem 360mg d**
Ivabradine 5mg bd	-5.51 (unknown 95% CI)	-4.79 (unknown 95% CI)
Ivabradine 7.5mg bd	-4.09 (unknown 95% CI)	-5.89 (unknown 95% CI)

Heart-rate reduction was not directly a patient relevant outcome, nor was it specified as a primary outcome in the trials. The need to accept that heart-rate is a valid surrogate for mortality, and that a reduction in heart rate alone (through medication) causes a reduction in mortality, underpinned the entire submission.

Results of indirect comparisons and other pooled analyses on which economic evaluation is based

Study	**Ivabradine HR reduction (bpm), (95%CI)**	**Diltiazem HR reduction (bpm).** No CIs provided	**Incremental difference**
Indirect comparison [a] via placebo	Adjusted -9.91 [c] (-14.48, -5.34)	Adjusted -4.40 [d] Adjusted -5.12 [e]	-5.51 [d] -4.79 [e]
Indirect comparison [b] via amlodipine	Adjusted -11.09 (-12.58, -9.59)	Adjusted -7.0 [d] Adjusted -5.2 [e]	-4.09 [d] -5.89 [e]
CAR 1 post-hoc sub-group analysis: HR ≥75 bpm	Unadjusted -16.56 (-17.43, -15.69)	-	
Diltiazem meta-analysis [f], HR 74-84		Unadjusted: -6.1 Adjusted -3.9	
Diltiazem meta-analysis [f], HR ≥85		Unadjusted: -10.7 Adjusted -4.9	
Economic Evaluation	Uses CAR-1 results (above)	Arbitrary values: -3, -4, -5 or -6	-13.56 to -10.36

[a] ivabradine 5mg bd (from CL2-009), [b] ivabradine 7.5mg bd (from CL3-023), [c] In this study HR increased from baseline in placebo arm (making adjusted effect size > unadjusted effect size) whereas in all other studies HR decreased in placebo or comparator arm (making adjusted effect sizes < unadjusted effect sizes); [d] vs diltiazem 240mg (multiple studies, pooled), [e] vs diltiazem 360mg (multiple studies, pooled), [f] Boden et al.
HR = heart rate; bpm = beats per minute, CI = confidence intervals, CAR = Complementary Analyses Report (pooled results from 5 phase II/III studies of various design, including those used for the indirect comparisons, with extensive post hoc subgroup analyses)
Source: Compiled during the evaluation

Given the uncertainty of effect size around the diltiazem results, the submission used a range of arbitrary results that covered the plausible range in the economic evaluation.

The primary outcomes of the key ivabradine trials were (i) CL3-023 (vs amlodipine) total exercise duration from bicycle exercise tolerance tests, and (ii) CL2-009 (vs placebo) time to limiting angina and time to 1mm ST segment depression.

The PBAC noted that these results were reported, and appeared to show ivabradine was no worse than amlodipine, but were not the basis of the submission.

The submission presented new longer-term toxicity data which was not comparative.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission described ivabradine as

1) equivalent in terms of comparative effectiveness in the immediate outcome of exercise tolerance, and
2) superior in terms of comparative effectiveness in the outcome of heart-rate lowering (proposed as a surrogate for the long-term outcome of mortality), and
3) equivalent in terms of comparative safety compared to diltiazem.

The PBAC did not agree with this claim.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented updated modelled economic evaluations, based on new epidemiological data, new risk equations and revised estimates of treatment effect (for both ivabradine and the comparators). The submission presented 540 ICER calculations that ranged from less than $15,000 to $45,000 – $75,000 per incremental life-year gained.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be between 15,000 – 20,000 in Year 5, compared with less than 10,000 in the previous submission.

The submission estimated the financial cost per year to the PBS to be less than $5 million in Year 5. The PBAC considered this might be an underestimate given the offsets were relatively overestimated.

12. Recommendation and Reasons

The PBAC considered, that in the event listing were to be recommended on the basis requested by the sponsor, the restriction proposed by the Restrictions Working Group more appropriately defines the patient group for whom treatment is intended than the restriction proposed by the sponsor, noting that the former proposal is based on the restriction for topiramate in the recently PBS listed indication of migraine prophylaxis.

The Committee continued to have major concerns about the clinical positioning of ivabradine. Although the Committee agreed that diltiazem and amlodipine are reasonable comparators (in the pre-subcommittee response the sponsor asks the committee to focus on the comparison with amlodipine in preference over diltiazem), the PBAC reiterated its view that in the indication for which listing is sought, a comparison with the long acting nitrates is

also appropriate. Notwithstanding the submission's claim that there is no evidence that the nitrates lower heart rate or reduce mortality, patients will be prescribed ivabradine first and foremost because they have chronic stable angina and this fact alone makes a comparison with nitrates relevant.

The PBAC accepted, as previously, that with respect to short term outcomes (exercise tolerance, episodes angina), ivabradine appears non-inferior to amlodipine in controlling the symptoms of angina. The PBAC agreed that the indirect comparison of ivabradine and diltiazem in terms of improvements in exercise tolerance is difficult to interpret. Although the Committee considered that it is likely that ivabradine is superior to diltiazem in terms of heart rate reduction, its confidence in this finding was reduced by the lack of an appropriate error measurement or estimate of uncertainty in the indirect comparison and by the documented anomalies in the results of this comparison compared with the dose-response curve of diltiazem.

The Committee agreed with the sponsor that the comparison of ivabradine with amlodipine is based upon stronger evidence than the comparison of ivabradine with diltiazem. In recognition of this, the PBAC accepted that the comparison with amlodipine is more relevant for decision making in this context than the comparison with diltiazem.

However overall the PBAC agreed that it is difficult to understand how the submission can claim superiority of ivabradine in terms of mortality in angina patients, when it appears to be non-inferior and clearly not superior to amlodipine, on intermediate outcomes relating to angina symptoms. The efficacy advantages claimed by the submission remain uninterpretable in relation to the broader efficacy of ivabradine as an anti-anginal drug, and further clinical trial data relating to the effect of ivabradine on angina are required.

The current comparison with amlodipine does not support the higher price for ivabradine requested by the sponsor because of the uncertainties inherent in the post-hoc subgroup analyses CAR 1 and CAR 3. Additionally, this comparison also relies upon the assumption that the heart rate reduction achieved by ivabradine is a valid surrogate for mortality, and, as discussed below, PBAC continues to have doubts about the validity of this assumption.

The PBAC also remained concerned about the comparative toxicity of ivabradine and diltiazem, noting there are no direct comparative data on the toxicity profiles of the two drugs. Given its unique mechanism of action, ivabradine has a distinctly different toxicity profile to diltiazem and other anti-anginal agents, such that an assessment of relative toxicity concerns might best be considered through impact on quality of life.

In addition to the areas of clinical uncertainty described above, the PBAC continued to have concerns with the submission's use of the heart rate reduction outcome to support its claim that ivabradine represents a cost-effective treatment intervention compared to diltiazem or amlodipine. Although the new analyses using the CASS, CCHS and GPRN data as discussed in the pre-subcommittee response and at the hearing, go some way towards addressing the possible confounding effect of blood pressure reductions on the heart rate results from the Cucherat meta-analysis, they nonetheless rely upon a series of mathematical simulations which are based upon the results of diverse cohort studies. The direct effect of an ivabradine induced reduction in heart rate on the cardiovascular mortality of an individual patient remains highly uncertain. In other words, although it is accepted that individuals with a

lower heart rate per se have reduced cardiovascular mortality compared to those with a higher heart rate, and although the resubmission provides some reassurance that a reduction in heart rate may be associated with a reduction in mortality, there remains no direct evidence to show that a reduction in heart rate mediated by ivabradine reduces the mortality of patients with a high initial heart rate to that experienced by individuals with a lower baseline heart rate. This means that the cost-effectiveness analyses presented by the submission is only weakly supported and does not justify the price premium requested by the submission.

The Committee continued to consider that the results of the large long term outcome study (BEAUTIFUL) may better inform this issue, as patients with long term stable angina are likely to represent a significant proportion of subjects in the study.

The PBAC noted a number of other clinical and economic concerns with the data presented and agreed that they would need to be addressed in any future submission. The Committee noted the comment made by ESC about the drug zatebradine but decided that it was not relevant for its decision.

Therefore the PBAC rejected the submission because of incomplete evidence of comparative clinical effectiveness and safety for ivabradine with the appropriate comparators in the treatment of angina. Additionally there remains insufficient evidence to directly support the claim that ivabradine's putative superiority in reducing heart rate over diltiazem or amlodipine translates into reduced cardiovascular mortality, thus providing an insufficient basis to support the cost-effectiveness analysis presented.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor chose not to comment.