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: November 2007

1. Purpose of Application:

The submission sought an Authority required PBS listing for the treatment of chronic stable angina due to atherosclerotic coronary artery disease.

2. Background:

This drug had not previously been considered by the PBAC.

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:

IVABRADINE HYDROCHLORIDE
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.

For the PBAC's view of the requested restriction, 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.

6. Comparator:

The submission nominated the non-dihydropyridine calcium channel blocker (CCB), diltiazem as the main comparator and the dihydropyridine CCB, amlodipine as a minor comparator.

For PBAC's comments, see Recommendation and Reasons.

7. Clinical trials

The basis of the submission was:

- 9 randomised trials indirectly comparing ivabradine (7.5mg/5mg twice daily) and diltiazem (180mg to 360mg daily) using either amlodipine (2 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 were as follows:

Trial ID-Phase/ First author	Protocol title/ Publication title	Publication citation
Indirect comparison: common reference of placebo		

Ivabradine		
Fox,K (CL2-009) Borer (CL2-009)	Ivabradine: a selective and specific I_f inhibitor: efficacy and safety in stable angina Borer, J.S., Fox, K., Jaillon, P., Lerebours, G. Antianginal and antiischemic effects of ivabradine, an I_f inhibitor, in stable angina: a randomised, double-blind, multicentered, placebo-controlled trial	Eur Heart J 2003; 5(suppl):G36-G45 Circulation 2003;107(6):817-823
Diltiazem		
Go,M	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,F.K	Long-term study of high-dose diltiazem in chronic stable exertional angina	Am Heart J,1984; Vol 107:1215
Khurmi,N.S	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.	Translated title: Myocardial ischemia with stable angina pectoris:clinical ergometric evaluation with diltiazem	Arq Bras Cardiol, 1992; 58(2):149-55
Strauss,W.E	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	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	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	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		
Ruzyllo (CL3-023)	Ruzyllo, W., Tendera, M., Fox, K.M. 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-inferiority trial.	Drugs, 2007;67(3):393-405

8. Results of trials

Results of the indirect comparison for ivabradine (7.5mg bd) compared to diltiazem using amlodipine as the common comparator - change in heart rate at rest

Trial	Incremental heart rate change in bpm (SE) (95%CI)	Ivabradine heart rate change from baseline (SE) (95%CI)	Amlodipine heart rate change from baseline (SE) (95%CI)	Diltiazem heart rate change (SE) (95%CI)	Incremental heart rate change in bpm (SE) (95%CI)	Indirect estimate of effect Incremental heart rate (SE) (95%CI)

CL3-023	-11.00[a] (0.91) (-12.79, -9.22)	N=381 -11.2 (±12.5)	N= 398 *-0.2* *(±12.2)*			
Merchand[b], 1996			N=35 *3* *(NR)*	N=28 -4 (NR)	*-7* (NR)	**-7.20[‡]** ***-4*** **(NE)**
Chugh[c,d], 1984			N=33 *3.1* (NR)	N=34 -2.10 (NR)	*-5.20* (NR)	**-9.10[‡‡]** ***-5.8*** **(NE)**

[a] unadjusted for country and baseline heart rate; [b] diltiazem: 180mg per day in three divided doses for two weeks which was increased to 240mg per day in four divided doses, amlodipine: 5mg per day as a morning dose for two weeks which was increased to 10mg per day; [c] diltiazem: 240mg per day for two weeks which was then increased to 360mg per day, amlodipine: 5mg per day as a morning dose for two weeks which was increased to 10mg per day; [d] baseline heart rate at rest was higher for the diltiazem arm in Chugh et al (87.4bpm) compared to the ivabradine arm of CL3-023 (78bpm); [‡]calculated by the submission as ivabradine heart rate change (-11.20) minus diltiazem heart rate from Merchand (-4.00); [‡‡] calculated by the submission as ivabradine heart rate change (-11.20) minus diltiazem heart rate from Chugh (-2.10); bpm = beats per minute; NR = not reported in the published article (where standard errors of the change in heart rate from baseline are unavailable in the published diltiazem trial reports, the submission utilizes the standard errors of heart rate change from the ivabradine trials; NE = not evaluable; S.E = standard error; bd = twice daily; bpm = beats per minute; *Italics in the above table represent results adjusted for the common comparator calculated during the evaluation.*

Results of the indirect comparison for ivabradine 5.0mg bd compared to diltiazem 180-360mg/day using placebo as the common comparator - change in heart rate at rest

Trial	**Incremental heart rate change in bpm (SE) (95%CI)**	**Ivabradine heart rate change from baseline (SE) (95%CI)**	**Placebo heart rate change from baseline (SE) (95%CI)**	**Diltiazem heart rate change (SE) (95%CI)**	**Incremental heart rate change in bpm (SE) (95%CI)**	**Indirect estimate of effect Incremental heart rate (SE) (95%CI)**
CL2-009	-9.91 *(1.93)* *(-14.48, -5.34)* [a]	N=59 -9.54 (±11.95)	*N= 68* *0.37* *(±10.88)*			
Maranhao[b], 1991			*N=43* *-1.5 (NR)*	N=44 *-5.90* (NR)	-4.40 [c] (NR)	
Khurmi[d], 1984			*N=33 CD* *(NR)*	N=17*CD*	-5.20 [c] (NR)	
Hossack[e], 1984			*N=15* *CD* *(NR)*	N=15 *CD*	-3.66[c] (NR)	
Go[f] 1984			*N=11* *CD* *(NR)*	N=11 *CD* *(NR)*	-7.0 (NR)	
Weighted[g] heart rate reduction at rest in beats per minute Mean (S.E.)	-9.91 *(1.93)* *(-14.48, -5.34)* [a]				-5.12[‡] -4.40	-5.51 -4.79

[a]Dunnett's 95% confidence interval for active versus placebo; ,[b] patients received diltiazem doses ranging from 180mg/day to 240mg/day; [c]could not be verified from the published report, [d]dose of diltiazem ranged from 60mg three times a day to 120mg three times a day; [e]patients received diltiazem 360mg/day; [f]all patients received diltiazem, 30mg tablets at increasing doses: first week - placebo, second week – one tablet four times daily, third week – two tablets four times daily, fourth week – three tablets four times daily; [g]weighted according to sample size; [‡] -the submission calculates 1) the value of -5.12 after exclusion of the lower diltiazem dose study, Maranhao (1991), and 2) the value of -4.40 considering only the lower diltiazem dose study

Maranhao (1991); bpm = beats per minute; NR = not reported in the published article (where standard errors of the change in heart rate from baseline are unavailable in the published diltiazem trial reports, the submission utilizes the standard errors of heart rate change from the ivabradine trials; CD = could not be determined from the published report;

The direct comparison results between ivabradine and amlodipine - Exercise tolerance test parameters at baseline and 3 months in the intention-to-treat population, measured at trough of drug activity - are below:

Variable	Amlodipine 10mg od (n = 398)	Ivabradine 7.5mg bid (n = 381)	Difference vs amlodipine, E (SE)[a] [95% CI]	p-Value for noninferiority
Total exercise duration (sec)				
Baseline	400.1 ± 131.9	414.4 ± 133.0		
3 months	431.2 ± 140.9	442.0 ± 154.4		
Change at 3 months	31.2 ± 92.0	27.6 ± 91.7	−1.8 (6.6) [−14.6, 11.1]	<0.001
Time to angina onset (sec)				
Baseline	313.0 ± 121.8	325.2 ± 119.9		
3 months	379.5 ± 143.2	389.9 ± 156.4		
Change at 3 months	66.6 ± 99.1	64.7 ± 104.9	−0.6 (7.4) [−15.2, 14.0]	<0.001
Time to 1mm ST-segment depression (sec)				
Baseline	347.4 ± 123.9	355.0 ± 122.4		
3 months	387.1 ± 138.4	400.0 ± 152.2		
Change at 3 months	39.7 ± 103.2	44.9 ± 98.6	6.5 (7.2) [−7.6, 20.6]	<0.001

[a] E (SE) = estimate and CI is of the difference between ivabradine effect and amlodipine effect, based on a covariance analysis adjusted on baseline and country factors. Other values are mean ± standard deviation**;** bid = twice daily; od = once daily; p-value for a non-inferiority margin of -30seconds.

Non-inferiority was established for time to angina onset, 1mm ST-segment depression and total exercise duration. Treatment with amlodipine 10mg and ivabradine 7.5mg similarly reduced short-acting nitrate consumption over three months.

Changes in heart rate and rate-pressure product (mean ± standard deviation) at 3 months in the intention-to-treat population, measured at trough of drug activity

Variable	Amlodipine 10mg od (n = 398)	Ivabradine 7.5mg bid (n = 381)	Difference vs amlodipine E (SE)[a] [95% CI]
Heart rate at rest			
Baseline	78.8 ± 13.4	78.6 ± 13.0	
3 months	78.6 ± 13.2	67.4 ± 11.8	
Change at 3 months	−0.2 ± 12.2	−11.2 ± 12.5	−11.1 (0.8)
[95% CI][b]	[−1.5, 1.0]	[−12.5, −10.0]	[−12.6, −9.6]
p-Value[c] vs baseline	p = 0.720	p < 0.001	
p-Value[d] vs amlodipine		p < 0.001	
Heart rate at peak of exercise			
Baseline	131.0 ± 18.4	132.1 ± 18.9	
3 months	130.8 ± 17.5	119.7 ± 7.1	
Change at 3 months	−0.2 ± 12.8	−12.4 ± 15.3	−11.8 (0.9)
[95% CI][b]	[−1.6, 1.3]	[−13.9, −11.0]	[−13.6, −10.1]
p-Value[c] vs baseline	p = 0.829	p < 0.001	
p-Value[d] vs amlodipine		p < 0.001	
Rate-pressure product at rest			
Baseline	10 377 ± 2 284	10 437 ± 2 282	
3 months	9 827 ± 2 112	8 990 ± 2 019	
Change at 3 months	−550 ± 1 978	−1 447 ± 2 071	−865 (122)
[95% CI][b]	[−756, −344]	[−1 658, −1 236]	[−1 105, −625]
p-Value[c] vs baseline	p < 0.001	p < 0.001	
p-Value[d] vs amlodipine		p < 0.001	
Rate-pressure product at peak of exercise			
Baseline	23 483 ± 5 084	23 850 ± 5 203	
3 months	23 012 ± 4 955	21 925 ± 5 002	
Change at 3 months	−471 ± 4 042	−1 926 ± 3 848	−1 325 (258)
[95% CI][b]	[−865, −77]	[−2 328, −1 526]	[−1 831, −819]
p-Value[c] vs baseline	p = 0.019	p < 0.001	
p-Value[d] vs amlodipine		p < 0.001	

[a] E (SE) and CI of the difference between ivabradine effect and amlodipine effect, based on a covariance analysis adjusted on baseline and country factors. Other values are mean ± standard deviation;
[b] CI of the change within treatment group based on an analysis of variance without adjustment.
[c] Student's t-test based on the overall general linear model (least-squares norm);
[d] Student's t-test based on the overall general linear model (least-squares norm) with baseline as a covariate and country as a random factor; bid = twice daily; CI = confidence interval; E (SE) = estimate (standard error); od = once daily; *heart rates in beats per minute.*

The submission did not provide any indirect estimates of the relative safety of ivabradine and diltiazem. For the comparative safety between ivabradine and amlodipine, there were more adverse events reported in the ivabradine 7.5mg twice daily group than in the amlodipine 10mg once daily group. The PBAC noted there was inadequate evidence to support any claim of equivalent safety between ivabradine and diltiazem. The PBAC also noted that the comparative safety data between ivabradine and amlodipine were difficult to interpret due to the different treatment periods in the ivabradine and amlodipine arms and the unblinded ascertainment of safety outcomes.

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

9. Clinical Claim

The submission described ivabradine as having superiority in heart rate reduction over diltiazem, its main comparator and having similar or less toxicity; the submission described ivabradine as having superiority in heart rate reduction and similar improvement in exercise tolerance tests over its minor comparator, amlodipine, and having similar or less toxicity.

For PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

The submission did not present a trial-based economic evaluation. This was considered reasonable given that the evidence for the main comparator was based on a comparison of multiple trials where surrogate outcomes (heart rate reduction) were measured and resources were not reported.

The submission presented a modelled economic evaluation. The resources included were drug costs and costs of cardiac events – myocardial infarction (MI), stroke, chronic heart failure (CHF) and cardiac surgery.

The modelled incremental discounted cost per extra discounted QALY, at 5 years treatment, was estimated as follows:
ivabradine 7.5mg vs (generic) diltiazem 360mg: between $45,000 - $75,000;
ivabradine 5mg vs (generic) diltiazem 240mg: between $45,000 - $75,000
ivabradine 7.5mg vs amlodipine 10mg: between $15,000 - $45,000

As the PBAC did not accept the clinical claim of superiority, the PBAC did not accept the validity of the economic analysis, *see Recommendation and Reasons.*

11. Estimated PBS Usage and Financial Implications:

The financial cost per year to the PBS minus any savings in use of other drugs was estimated to be less than $10 million in Year 5.

12. Recommendation and Reasons:

The PBAC noted that the submission had nominated the non-dihydropyridine calcium channel blocker (CCB), diltiazem as the main comparator and the dihydropyridine CCB, amlodipine, as a minor comparator. The PBAC agreed with the ESC that an additional comparison with the long-acting nitrates would be appropriate, as in the absence of clinical endpoint data for ivabradine it is most likely to be used third line after beta-blockers and non-dihydropyridine CCBs, and thus to compete with the dihydropyridine CCBs and the long-acting nitrates.

The Committee noted that the indirect efficacy comparison between ivabradine and diltiazem presented in the submission was difficult to interpret. Further, there is inadequate evidence in the submission to support any claim of equivalent safety between ivabradine and diltiazem.

The Committee agreed with the submission that ivabradine 7.5mg twice daily appears to have comparable clinical efficacy in controlling the symptoms of angina compared to amlodipine 10mg once daily. The comparative safety data for ivabradine and amlodipine were difficult to interpret due to the different treatment periods in the ivabradine and amlodipine arms and the unblinded ascertainment of safety outcomes.

The submission's choice of the heart rate reduction outcome to support the claim that ivabradine is superior to diltiazem and/or amlodipine is of critical importance and the PBAC did not accept this approach, particularly as these three drugs assert there effects through different means.

The submissions use of heart rate as a surrogate for mortality in the economic model was also not accepted by the PBAC.The PBAC further noted that a number of other clinical and economic concerns with the data presented had been raised during the evaluation and agreed that they needed to be addressed in any future submissions.

Thus, overall, the Committee rejected the application 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 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.