PUBLIC SUMMARY DOCUMENT
Product: IVABRADINE, tablet, 5 mg and 7.5 mg (as hydrochloride), Coralan®
Sponsor: Servier Laboratories (Australia) Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application

Re-submission to request an Authority Required listing for the treatment of symptomatic systolic heart failure in patients in sinus rhythm, with a heart rate of at least 75 beats per minute (bpm), measured after 5 minutes rest, who are stabilised on optimal heart failure therapy, which must include an ACE inhibitor or angiotensin II antagonist and a beta blocker (unless intolerant or contraindicated).

2. Background

At the November 2011 meeting, the PBAC rejected the submission for ivabradine for an Authority Required listing for the treatment of symptomatic systolic heart failure in patients in sinus rhythm, with a heart rate at or above 70 bpm stabilised on conventional therapy, which includes a beta blocker (unless intolerant or contraindicated) at a maximum tolerated dose because of the high uncertainty around the clinical evidence to support the clinical claim and the resultant high uncertainty in the economic analysis.

3. Registration Status

At the time of the PBAC consideration, ivabradine was not registered by the TGA for the requested indication.

Ivabradine was registered by the TGA on 27 August 2012 for the indication:

> Treatment of chronic heart failure - Treatment of symptomatic chronic heart failure of NYHA Classes II or III and with documented left ventricular ejection fraction (LVEF) less than or equal to 35% in adult patients in sinus rhythm and with heart rate at or above 77 bpm, in combination with optimal standard chronic heart failure treatment.

Ivabradine is also registered by the TGA for:

> Treatment of coronary artery disease - 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, OR in combination with atenolol 50 mg once daily when heart rate is at or above 60 bpm and angina is inadequately controlled.

4. Listing Requested and PBAC's View

Authority Required

Symptomatic systolic heart failure in a patient in sinus rhythm, with heart rate of at least 75 bpm, measured after 5 minutes rest, who is stabilised on optimal heart failure therapy, which must include an ACE inhibitor, or angiotensin II antagonist and a beta-blocker, if tolerated.

Or, in a patient who has contraindication and/or intolerance to beta-blockers as described in the relevant TGA-approved Product Information, details of the contraindication and/or intolerance must be provided at the time of application.

Note

Continuing Therapy Only:

For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

The sponsor's pre-PBAC response proposed amendments to the requested listing in line with the TGA approved indication, "treatment of symptomatic chronic heart failure of NYHA classes II or III and with documented left ventricular ejection fraction (LVEF) of less than or equal to 35% in adult patients in sinus rhythm and with a heart rate at or above 77 bpm, in combination with optimal standard chronic heart failure treatment".

However, the PBAC raised questions about the feasibility of implementing such a restriction should the product be listed. The PBAC further noted that changing the originally requested baseline heart rate of at least 75 bpm to the TGA-approved and pre-specified subgroup with heart rate of at least 77 bpm decreases the patient population by 20%. The PBAC considered that the effect of the restriction changes on the estimates of PBS usage and the resultant financial implications will need to be clarified.

5. Clinical Place for the Proposed Therapy

Chronic heart failure (CHF) is associated with recurrent and life-threatening decompensatory episodes, exacerbations of concurrent disease states (e.g. respiratory failure or renal failure) and has a worse prognosis than many forms of cancer. The prevalence of CHF increases with age. Common causes of CHF are ischaemic heart disease, hypertension, valvular heart disease, (stenosis or regurgitation) and idiopathic dilated cardiomyopathy. Early symptoms include exertional dyspnoea and fatigue, with orthopnoea, paroxysmal nocturnal dyspnoea and ankle oedema occurring later. Less obvious symptoms include persistent cough, especially when supine or nocturnal, fatigue, nausea and anorexia.

Management of CHF aims to improve symptoms and reduce hospitalisations and mortality. Patients with CHF should be treated with an angiotension-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and a beta-blockers as these treatments have been demonstrated to reduce mortality.

6. Comparator

The submission nominated placebo (standard medical management) as the main comparator.

The PBAC agreed that placebo (standard medical management) is the appropriate comparator for ivabradine in the requested third-line setting.

7. Clinical Trials

No changes have been made to the SHIfT trial data presented in the previous submission.

An additional post-hoc subgroup analysis was provided in the re-submission, which included patients with both a heart rate of ≥75 beats per minute (bpm) and receiving ≥50% target β-blocker dose.

Details of the trials and associated reports published at the time of submission are in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation

Ivabradine trials vs placebo		
SHIfT - Study CL3-16257-063		
Komajda M and Swedberg K, 2010	Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction: SHIfT study. A three-year randomised double-blind placebo-controlled international multicentre study. 21 October 2010.	Clinical Study Report: CL3-16257-063 - Laboratories Servier
Chassany O and I Ekman, 2011	Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction. A three-year randomised double-blind placebo-controlled international multicentre study.	Patient-reported outcomes sub-study to the clinical study CL3-16257-063.
Swedberg K, M Komajda et al, 2010	Ivabradine and outcomes in chronic heart failure (SHIfT): A randomised placebo-controlled study.	*The Lancet* 2010b; 376(9744): 875-885.
Swedberg K, M Komajda et al, 2010	Erratum: Ivabradine and outcomes in chronic heart failure (SHIfT): A randomised placebo-controlled study (Lancet (2010) 376 (875-885)).	*The Lancet* 2010c: 376(9757): 1988.
Bohm M, K Swedberg et al, 2010	Heart rate as a risk factor in chronic heart failure (SHIfT): The association between heart rate and outcomes in a randomised placebo-controlled trial.	*The Lancet* 2010: 376(9744): 886-894.
Swedberg K, M Komajda et al, 2010	Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: The Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIfT).	*European Journal of Heart Failure* 2010a: 12(1): 75-81.
Ekman I, Chassany O et al, 2011	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* 32(19): 2395-2404
Tardif J C, Omeara E et al, 2011	Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: Results from the SHIFT echocardiography substudy.	*European Heart Journal* 32(20): 2507-2515

8. Results of Trials

The resubmission presented the key results for the primary outcome, a composite endpoint of cardiovascular (CV) death or hospitalisation for worsening HF, for both the ITT and post-hoc heart rate ≥75 bpm populations from the SHIfT trial. These are presented in the table below. The results for patients with a heart rate ≥75 bpm was relevant for the restriction (n=4150) proposed prior to TGA registration.

Also included in the resubmission, were the results from SHIfT on an additional post-hoc sub-group of patients with both a heart rate of ≥75 bpm and receiving ≥ 50% target β-blocker dose.

Outcomes[a]	**Ivabradine n/N (%)**	**Placebo n/N (%)**	**HR[b] (95% CI)**	**p-value**	**RD**	**NNT [95% CI]**
Primary composite endpoint - CV death or hospitalisation for worse heart failure						
ITT	793/3241 (24.5)	937/3264 (28.7)	**0.82 (0.75, 0.90)**	**<0.0001**	**4.2%**	**24 *[16,48]***
≥75 bpm	545/2052 (26.6)	688/2098 (32.8)	**0.76 (0.68, 0.85)**	**<0.0001**	**6.2%**	***16 [11,29]***

Outcomes[a]	Ivabradine n/N (%)	Placebo n/N (%)	HR[b] (95% CI)	p-value	RD	NNT [95% CI]
Component endpoints						
CV death						
ITT	449/3241 (13.9)	491/3264 (15.0)	0.91 (0.80, 1.03)	0.128	1.2%	84 *[35,193]*
≥75 bpm	304/2052 (14.8)	364/2098 (17.4)	**0.83 (0.71, 0.97)**	**0.0166**	**2.5%**	***39 [21,333]***
Hospitalisation for worsening heart failure						
ITT	514/3241 (15.9)	672/3264 (20.6)	**0.74 (0.66, 0.83)**	**<0.0001**	**4.7%**	**21 *[15, 35]***
≥75 bpm	363/2052 (17.7)	503/2098 (24.0)	**0.70 (0.61, 0.80)**	**<0.0001**	**6.3%**	***16 [11, 26]***

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; NNT = number needed to treat; RD = risk reduction; n/c = not calculable; **bold** = statistically significant

[a] All outcomes were observed over a median follow-up of 22.9 months.

[b]Estimate of the HR between treatment groups based on an adjusted Cox proportional hazards model with β-blocker intake at randomisation as a covariate

95% CIs of NNT were calculated during the evaluation.

The results for the SHIfT ITT population (heart rate of at least 70 bpm) showed that ivabradine was associated with an 18% reduction in risk for the primary composite endpoint of cardiovascular death or hospitalisations for worsening heart failure (HR 0.82 [95% CI: 0.75, 0.90; p<0.0001]; the estimate of absolute risk difference was 4.2). However, the results for the component endpoints were only statistically significant for heart failure hospitalisations, and not for cardiovascular death.

For patients with a baseline heart rate ≥75 bpm (N=4,150) and with a mean follow-up period of 22 months, ivabradine was associated with a 24% reduction in the risk of CV death or HF hospitalisation (hazard ratio (HR): 0.76 (95% confidence interval (CI): [0.68, 0.85]). The statistical significance of the primary composite endpoint was driven by the component of HF hospitalisation, rather than by CV mortality. Median survival could not be estimated.

For the post-hoc subgroup of patients with heart rate of at least 75 bpm and receiving at least 50% target beta-blocker dose, there was no statistically significant difference for the primary composite endpoint or cardiovascular death. Treatment with ivabradine was associated with a statistically significant reduction in risk for heart failure hospitalisations for this subgroup.

The submission also presented clinical data and economic analyses for the pre-specified subgroup of patients with a heart rate of at least 77 bpm.

For the pre-specified subgroup of patients with heart rate of at least 77 bpm (N=3,357) in SHIfT, treatment with ivabradine resulted in a statistically significant reduction in the primary composite endpoint (HR 0.75 [95% CI: 0.67, 0.85; p=0.029]). The component endpoints of heart failure hospitalisations and cardiovascular death were also statistically significant (HR 0.69 [95% CI: 0.59, 0.80; p<0.0001] and HR 0.81 [95% CI: 0.69, 0.96; p=0.038] respectively). Results for the post-hoc subgroup of patients with heart rate of at least 77 bpm and receiving at least 50% target beta blocker dose were only significant for the component outcome of heart failure hospitalisations.

For PBAC's view of these results, see Recommendation and Reasons.

The re-submission stated that ivabradine-related AEs are tolerated. Over the trial period median follow-up of 22.9 months, the incidence of adverse events (AEs) in the subgroup of participants that had a heart rate of ≥75 bpm at baseline was 76.0%, similar to the placebo group, 76.7%. Most rates of AEs were similar between ivabradine and placebo for both the safety set and the subgroup with heart rate ≥75 bpm. No data were provided for the ≥75 bpm subgroup for treatment-related AEs. AEs were slightly higher for ivabradine in the whole population and similar for the ≥75 bpm sub-group. Ivabradine treatment was associated with a small but significantly higher risk 3.4% (95%CI: 2.5%, 4.4%) for symptomatic bradycardia and a 2.3% (95%CI: 1.5%, 3.0%) higher risk for phosphenes.

9. Clinical Claim

The submission described ivabradine as superior in terms of comparative benefit and equivalent in terms of comparative safety over placebo for patients with a baseline heart rate of ≥75 bpm.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A modelled economic evaluation based on a superiority claim for comparative benefit was presented in the re-submission. The model was unchanged from the previous submission.

A revised base case was modelled during the evaluation using the efficacy results for the post-hoc subgroup of patients who have both a heart rate at baseline of at least 75 bpm and are using at least 50% of the β-blocker target.

The results of the revised base case indicate the ICER is highly sensitive to small changes in the relative rate of hospitalisations for worsening HF. When patients with both HR ≥75 bpm and at least 50% are receiving target β-blocker therapy, the ICER increased by 65%. Using the 95% CIs from the SHIfT Cox proportional hazards modelling results, the revised ICER ranged from less than $15,000 to greater than $200,000. The cost-effectiveness results are highly uncertain.

The PBAC noted the reduced ivabradine price offered in the pre-PBAC response to address the uncertainty identified by the ESC associated with hospitalisations reduced the ICER. However, the PBAC noted that this revised ICER, and additional sensitivity analyses presented in the pre-PBAC response were not able to be verified in the available time and therefore was not prepared to accept the revised analysis until it was evaluated.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients treated to be in the range of 10,000 – 50,000 in Year 5 of listing.

The estimate was based on current β-blocker use statistics from PBS data. The submission's estimate was uncertain due to the assumptions made during calculations, namely, the potential underestimate of the number of HF patients in Australia and proportion of those on subsidised β-blocker therapy. A revised estimate was undertaken in the evaluation and based on figures presented by DUSC in October 2011

The submission estimated the net cost to Government to be in the range of $10 – $30 million by Year 5 of listing.

12. Recommendation and Reasons

The PBAC agreed that placebo (standard medical management) is the appropriate comparator for ivabradine in the requested third-line setting.

The PBAC noted the advice in the sponsor's pre-PBAC response that ivabradine had been recommended for approval by the TGA for the indication "treatment of symptomatic chronic heart failure of NYHA classes II or III and with documented left ventricular ejection fraction (LVEF) of less than or equal to 35% in adult patients in sinus rhythm and with a heart rate at or above 77 bpm, in combination with optimal standard chronic heart failure treatment". The PBAC noted that the pre-PBAC response proposed amendments to the requested listing in line with the TGA approved indication. The PBAC acknowledged the sponsor's willingness to work with the Committee and the Restrictions Working Group in order to finalise an appropriate restriction wording. The PBAC further noted that changing the originally requested baseline heart rate of at least 75 bpm to the TGA-approved and pre-specified subgroup with heart rate of at least 77 bpm decreases the patient population by 20%. The PBAC considered that the effect of the restriction changes on the estimates of PBS usage and the resultant financial implications will need to be clarified. The PBAC also raised questions about the feasibility of implementing such a restriction should the product be listed.

As in the previous submission, the resubmission presented the SHIfT trial comparing ivabradine with placebo in heart failure patients with systolic dysfunction. Compared to the previous submission, the resubmission presented an additional post-hoc subgroup analysis of patients with heart rate of at least 75 bpm and receiving at least 50% target beta-blocker dose. The submission also presented clinical data and economic analyses for the pre-specified subgroup of patients with a heart rate of at least 77 bpm.

The results for the SHIfT ITT population (heart rate of at least 70 bpm) showed that ivabradine was associated with an 18% reduction in risk for the primary composite endpoint of cardiovascular death or hospitalisations for worsening heart failure (HR 0.82 [95% CI: 0.75, 0.90; p<0.0001]; the estimate of absolute risk difference was 4.2). However, the results for the component endpoints were only statistically significant for heart failure hospitalisations, and not for cardiovascular death. For the post-hoc subgroup of patients with heart rate of at least 75 bpm and receiving at least 50% target beta-blocker dose, there was no statistically significant difference for the primary composite endpoint or cardiovascular death. Treatment with ivabradine was associated with a statistically significant reduction in risk for heart failure hospitalisations for this subgroup.

For the pre-specified subgroup of patients with heart rate of at least 77 bpm in SHIfT, treatment with ivabradine resulted in a statistically significant reduction in the primary composite endpoint (HR 0.75 [95% CI: 0.67, 0.85; p=0.029]). The component endpoints of heart failure hospitalisations and cardiovascular death were also statistically significant (HR 0.69 [95% CI: 0.59, 0.80; p<0.0001] and HR 0.81 [95% CI: 0.69, 0.96; p=0.038] respectively). Results for the subgroup of patients with heart rate of at least 77 bpm and receiving at least 50% target beta blocker dose were only significant for the component outcome of heart failure hospitalisations.

Overall, the PBAC accepted that there may be evidence of a benefit associated with ivabradine treatment in a pre-specified sub-group of patients, (n=3,357) but remained concerned that this effect is in a subgroup only, and that it is driven by the events related to hospitalisation.

The PBAC noted from the sponsor's pre-PBAC response, that the percentage of PBS patients treated with at least 50% target beta blocker dose was similar to the percentage in the SHIfT population. The SHIfT subgroup with heart rate threshold of 77 bpm without further restriction based on beta blocker dose might be representative of the likely PBS population but other demographic characteristics of the trial subgroup, such as age and gender were much less clearly representative of the potential PBS target group.

The PBAC recalled its previous concerns regarding the statistical significance of the composite endpoint being driven by the clinician-decision component (i.e. heart failure hospitalisation), which may differ in Australian clinical practice compared to the largely Eastern European population in SHIfT. The PBAC noted the reduced ivabradine price offered in the pre-PBAC response to address the uncertainty associated with hospitalisations, which reduced the ICER. However, the PBAC noted that this revised ICER, and additional sensitivity analyses presented in the pre-PBAC response were not able to be verified in the available time and therefore was not prepared to accept the revised analysis until it was evaluated.

The PBAC therefore deferred the submission to allow verification of the revised ICERs and clarification of the estimates of usage and cost to the PBS resulting from the proposed restriction changes, as well as an assessment of the feasibility of the proposed restriction.

Recommendation:
Defer

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

A minor submission for ivabradine will be considered at the November 2012 PBAC meeting