PUBLIC SUMMARY DOCUMENT
Product: Nebivolol hydrochloride, tablets, titration pack containing 42 tablets 1.25mg and 14 tablets 5 mg, 1.25 mg, 5 mg and 10 mg (base), Nebilet®
Sponsor: CSL Limited
Date of PBAC Consideration: November 2009

1. Purpose of Application
The submission sought an Authority required (STREAMLINED) listing for moderate to severe heart failure in a patient stabilised on conventional therapy which must include an ACE inhibitor (if tolerated).

2. Background
This drug had not previously been considered by the PBAC.

3. Registration Status
Nebivolol was TGA registered on 26 June 2009 for the treatment of essential hypertension and stable chronic heart failure as an adjunct to standard therapies in patients 70 years or older.

4. Listing Requested and PBAC's View
Authority required (STREAMLINED)
Moderate to severe heart failure stabilised on conventional therapy which must include an ACE inhibitor if tolerated.

NOTE: Nebivolol is indicated for the treatment of stable chronic heart failure as an adjunct to standard therapies in patients 70 years or older.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Many patients with clinical heart failure require combination therapy with an angiotensin converting enzyme (ACE) inhibitor, a beta blocker and a diuretic.

Nebivolol would be an alternative beta-blocker treatment option for heart failure patients aged 70 years and older.

6. Comparator
The submission nominated carvedilol, bisoprolol and metoprolol as the main comparators, which was considered appropriate.

7. Clinical Trials
The submission presented three direct randomised trials, Patrianakos 2005, Lombardo 2006, Marazzi 2007, comparing nebivolol and carvedilol; two of which used half the recommended dose of nebivolol (Patrianakos 2005, Lombardo 2006) and all used the recommended dose of carvedilol. The outcomes of the direct randomised trials were percentage increase in left ventricular ejection fraction (LVEF) and the six minute walk test (6MWT), which were considered to be surrogate outcomes.

The evidence for patient relevant clinical outcomes such as hospitalisations and mortality was based on an indirect comparison of six placebo-controlled trials, nebivolol, SENIORS; carvedilol, COPERNICUS, Carvedilol US, Carvedilol ANZ; bisoprolol, CIBIS-II; metoprolol, MERIT-HF. The baseline characteristics of patients in the SENIORS trial differed to that of the baseline characteristics of patients in the placebo-controlled trials for the carvedilol, bisoprolol and metoprolol trials.

The submission further provided the results of a post-hoc subgroup of patients from the SENIORS trial, referred to as SENIORS Subgroup in which, the patient baseline characteristics appeared to be more similar to those of the comparator trials. Although mean age remained higher and the proportion of men was somewhat lower, the LVEF function in the SENIORS Subgroup was similar to that of participants in the Carvedilol ANZ, CIBIS-II and MERIT-HF trials.

The table below shows the publication details of trials presented in the submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Patrianakos, et al. 2005	Comparative efficacy of nebivolol versus carvedilol on left ventricular function and exercise capacity in patients with nonischemic dilated cardiomyopathy. A 12-month study.	American Heart Journal, 2005, 150(5): 985.
Lombardo et al. 2006	Effects of nebivolol versus carvedilol on left ventricular function in patients with chronic heart failure and reduced left ventricular systolic function.	American Journal of Cardiovascular Drugs, 2006, 6(4): 259-263.
Marazzi et al. 2007	Effects of nebivolol versus carvedilol in hypertensive patients with chronic heart failure.	Circulation, 2007, 116, II_551.
SENIORS Shibata MC et al.	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS). Rationale and design.	International Journal of Cardiology, 2002, 86(1): 77-85.
Flather MD, et al.	Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS).	European Heart Journal, 2005, 26(3): 215-225
Ghio S, et al.	Effects of nebivolol in elderly heart failure patients with or without systolic left ventricular dysfunction: results of the SENIORS echocardiographic substudy.	European Heart Journal, 2006, 27(5): 562-568.
Dobre D, et al.	Tolerability and dose-related effects of nebivolol in elderly patients with heart failure: data from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial.	American Heart Journal, 2007, 154 (1): 109-115.
COPERNICUS Packer M, et al	Effect of carvedilol on survival in severe chronic heart failure.	New England Journal of Medicine, 2001, 344(22): 1651-1658.
Packer M, et al	Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study.	Circulation, 2002, 106(17): 2194-2199.
Zaikin SY et al.	Long term use of a non-selective beta-blocker with vasodilating properties carvedilol in patients with severe heart failure.	Kardiologiia, 2002, 42(4): 33-36.
Carvedilol US Packer M et al.	The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S.	New England Journal of Medicine, 1996,

	Carvedilol Heart Failure Study Group.	334(21): 1349-1355.
Fowler MB, et al.	Influence of carvedilol on hospitalizations in heart failure: incidence, resource utilization and costs. U.S. Carvedilol Heart Failure Study Group.	Journal of the American College of Cardiology, 2001, 37(6): 1692-1699.
Packer M et al.	Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise.	Circulation, 1996, 94(11): 2793-2799.
Bristow MR, et al.	Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators.	Circulation, 1996, 94(11): 2807-2816.
Colucci WS, et al.	Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group.	Circulation, 1996, 94(11): 2800-2806.
Cohn JN, et al.	Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group.	Journal of Cardiac Failure, 1997, 3(3): 173-179.
Carvedilol ANZ Australia-New Zealand Heart Failure Research Collaborative Group.	Effects of carvedilol, a vasodilator-beta-blocker, in patients with congestive heart failure due to ischemic heart disease.	Circulation, 1995, 92(2): 212-218.
	Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease.	Lancet, 1997, 349(9049): 375-380.
Doughty RN, et al.	Effects of carvedilol on left ventricular regional wall motion in patients with heart failure caused by ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group.	Journal of Cardiac Failure, 2000, 6(1): 11-18.
Richards AM, et al.	Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. Australia-New Zealand Heart Failure Group.	Journal of the American College of Cardiology, 2001, 37(7): 1781-1787.
CIBIS II Investigators and Committees	The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial.	Lancet, 1999, 353(9146): 9-13.
Erdmann E, et al.	Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure.	European Journal of Heart Failure, 2001, 3(4): 469-479.
Simon T, et al.	Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II).	Circulation, 2001, 103(3): 375-380.
Funck-Brentano C, et al.	Predictors of medical events and of their competitive interactions in the Cardiac Insufficiency Bisoprolol Study 2 (CIBIS-2).	American Heart Journal, 2001, 142(6): 989-997.
Simon T, et al.	Bisoprolol dose-response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency bisoprolol study(CIBIS II).	European Heart Journal, 2003, 24(6): 552-559.
MERIT-HF Study Group.	Rationale, design, and organization of the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF).	American Journal of Cardiology, 1997, 80(9B): 54J-58J.
	Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF).	Lancet, 1999, 353(9169): 2001-2007.
Goldstein S, et	The mortality effect of metoprolol CR/XL in patients	Clinical Cardiology,

al.	with heart failure: results of the MERIT-HF Trial.	1999, 22 Suppl 5V30-V35.
Hjalmarson A, et al.	Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group.	Journal of the American Medical Association, 2000, 283(10): 1295-1302.
Wikstrand J.	MERIT-HF--description of the trial.	Basic Research in Cardiology, 2000, 95 Suppl 1I90-I97.
Groenning BA, et al.	Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure.	Journal of the American College of Cardiology, 2000, 36(7): 2072-2080.
Groenning BA, et al	Antiremodeling effects on the left ventricle during beta-blockage with metaprolol in the treatment of chronic heart failure.	Congestive Heart Failure, 2001, 7(1):58-59.
Hjalmarson A, et al.	MERIT-HF mortality and morbidity data.	Basic Research in Cardiology, 2000, 95 Suppl 1 I98-103
Fagerberg B.	Screening, endpoint classification, and safety monitoring in the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF).	European Journal of Heart Failure, 2000, 2(3): 315-324.
Goldstein S, et al.	Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study.	Journal of the American College of Cardiology, 2001, 38(4): 932-938.
Gullestad L, et al.	Effect of metoprolol on cytokine levels in chronic heart failure--a substudy in the Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure (MERIT-HF).	American Heart Journal, 2001, 141(3): 418-421.
Gottlieb SS, et al.	Tolerability of beta-blocker initiation and titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF).	Circulation, 2002, 105(10): 1182-1188.
Ghali JK, et al	Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF).	Circulation, 2002, 105(13): 1585-1591.
Wikstrand J, et al.	How should subgroup analyses affect clinical practice? Insights from the Metoprolol Succinate Controlled-Release/Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF).	Cardiac Electrophysiology Review, 2003, 7(3): 264-275.
Deedwania PC, et al.	Efficacy, safety and tolerability of beta-adrenergic blockade with metoprolol CR/XL in elderly patients with heart failure.	European Heart Journal, 2004, 25(15): 1300-1309.
Deedwania PC, et al.	Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF.	American Heart Journal, 2005, 149(1): 159-167.
Ghali JK, et al.	The influence of renal function on clinical outcome and response to beta-blockade in systolic heart failure: insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF).	Journal of Cardiac Failure, 2009, 15(4): 310-318.

8. Results of Trials

The results of the surrogate outcomes of percentage increase in LVEF and the six minute walk test from the direct randomised trials and the percentage increase in LVEF results from SENIORS ECHO ≤35% and Carvedilol ANZ are shown below.

Trial	Endpoint (months)	Treatment effect[a] Difference in the change from endpoint to baseline (nebivolol – carvedilol) Difference (95% CI)
LVEF, % mean (SD)		
Patrianakos 2005	3	ΔδLVEF = -2.6 (NC) ΔδLVEF% = -16.8 (-29.7, -3.9)
	12	ΔδLVEF = -2.7 (NC) ΔδLVEF% = -14.8 (-27.5, -2.2)
Lombardo 2006	6	0 (NC)
Marazzi 2007	24	ΔδLVEF = -0.39 (-0.80, 0.03)[b] ΔδLVEF = -0.41 (-0.75, -0.07)[c]
SENIORS ECHO ≤35%	12	ΔδLVEF = 4.6 (1.3, 7.9) (nebivolol-placebo)
Carvediolol ANZ	6	ΔδLVEF = 5.2 (3.7, 6.8)[d] (carvedilol-placebo)
6 minute walk test, metres, mean (SD)		
Patrianakos 2005	-	NA
Lombardo 2006	6	-2 (NC)
Marazzi 2007	24	Δδ6MWT = -4.3 (-8.2, -0.3)[b] Δδ6MWT = -4.0 (-10.1, 2.1)[c]

NC=not calculable as SD not reported, δLVEF/6MWT=change in LVEF/6MWT from endpoint to baseline

[a] $\Delta\delta LVEF/6MWT = \delta LVEF/6MWT_{nebivolol} - \delta LVEF/6MWT_{carvedilol}$; $\Delta\delta LVEF\% = LVEF\%_{nebivolol} - LVEF\%_{carvedilol}$, calculated during the evaluation using RevMan 5

[b] adjusted for baseline LVEF or 6MWT. A statistically significant difference between groups at baseline for LVEF, no difference for 6MWT.

[c] unadjusted for baseline LVEF, 6MWT

[d] estimated by the submission

None of the direct randomised trials were designed as a non-inferiority trial. However, Marazzi, 2007 identified a difference in change in left ventricular ejection fraction (δLVEF) of 3% as clinically significant, consistent with previous studies comparing the effect of carvedilol and metoprolol on LVEF in patients with CHF. It was noted that in Marazzi (2007) a significant difference was observed in baseline LVEF between the groups ($p<0.001$), but no significant difference was observed in baseline six minute walk tests between the groups ($p=0.718$).

Both SENIORS ECHO and Carvedilol ANZ demonstrated that nebivolol and carvedilol, respectively, were superior to placebo in increasing LVEF.

In regard to toxicity comparisons, it was noted that each of the beta-blockers was associated with different adverse event profiles.

9. Clinical Claim

The submission claimed nebivolol to be non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over other beta blockers (carvedilol, bisoprolol and metoprolol).

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses are estimated as nebivolol 7.59 mg and carvedilol 37 mg, and by extension, bisoprolol 7.4 mg, metoprolol 138 mg. The estimates were based on the Marazzi (2007) trial. The PBAC accepted this.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year was estimated to be more than 200,000 in Year 5. This estimation was considered to be underestimated.

The financial savings per year to the PBS was estimated to be less than $5 million in Year 5. This estimation was considered to be overestimated.

12. Recommendation and Reasons

The PBAC recommended the Authority Required (STREAMLINED) PBS listing of nebivolol for moderate to severe heart failure in a patient stabilised on conventional therapy which must include an ACE inhibitor or Angiotensin II receptor antagonist (if tolerated), on a cost minimisation basis compared with carvedilol, bisoprolol and metoprolol. The equi-effective doses are estimated as nebivolol 7.59mg and carvedilol 37mg, and by extension, bisoprolol 7.4mg, metoprolol 138mg, based on the Marazzi (2007) trial.

Despite some concerns raised during the evaluation and by ESC that nebivolol may be less effective than the comparators, the PBAC accepted that nebivolol is no worse in terms of efficacy and safety than its pharmacological analogues carvedilol, bisoprolol and metoprolol. This was despite the fact that the claim of non-inferiority in the Marazzi (2007) was based on surrogate outcomes (change in LVEF, the six minute walk test and NYHA class improvement). Bisoprolol and metoprolol were listed on a cost-minimisation basis versus carvedilol based on final outcomes (mortality and hospitalisations). However, the PBAC noted that nebivolol is cheaper than the comparators and thus, on balance, could be recommended for listing.

The PBAC noted that the submission requested the restriction to include a NOTE stating "Nebivolol is indicated for the treatment of stable chronic heart failure as an adjunct to standard therapies in patients 70 years or older", based on the TGA approved indication. The PBAC considered that inclusion of such a NOTE could lead to potentially inappropriate promotion of nebivolol for older patients. Further, there was evidence in the submission that nebivolol is effective in patients younger than 70 years of age as well as over this age and this evidence may not have been available at the time of registration. The PBAC requested that the National Prescribing Service educate prescribers regarding these concerns.

The PBAC also recommended that the views of the sponsors of the listed beta-blockers be sought concerning the minor amendment to the restrictions to include the use of Angiotensin II receptor antagonists (as well as ACE-inhibitors) for consistency with the recommendation for nebivolol.

Recommendation:
NEBIVOLOL HYDROCHLORIDE, tablets, 1.25 mg, 5 mg and 10 mg (as hydrochloride), 28 tablet pack of 1.25 mg tablets, and titration pack containing 42 tablets 1.25 mg and 14 tablets 5 mg, Nebilet®, CSL Limited.

Restriction:	Authority Required (STREAMLINED) Moderate to severe heart failure in a patient stabilised on conventional therapy which must include an ACE inhibitor or Angiotensin II antagonist, if tolerated.
Maximum Quantity:	56 (1.25 mg) 28 (5 mg, 10 mg) #1 (1.25 mg (28); titration pack)
Repeats	5 (1.25 mg, 5 mg, 10 mg, and 1.25 mg (28)) 0 (titration pack)

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 has no comment.