PUBLIC SUMMARY DOCUMENT

Product: Duloxetine hydrochloride, capsule, 30 mg and 60 mg, Cymbalta®

Sponsor: Eli Lilly Australia Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought a restricted benefit PBS listing for treatment of major depressive disorder.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Duloxetine was registered by the TGA on 14 March 2007 for the treatment of major depressive disorder.

4. Listing Requested and PBAC's View

Restricted benefit

Major depressive disorders

See Recommendation and Reasons for the PBAC's View.

5. Clinical Place for the Proposed Therapy

Major depressive disorder is a major public health problem and is the most common mental disorder in Australia. Major depressive disorder is projected to be the second leading cause of mortality and disability worldwide by 2020.

Major depressive disorder is a common and chronic illness that is characteristically relapsing and remitting in nature with an estimated 50% of sufferers relapsing following resolution of a depressive episode. Estimates for lifetime prevalence range from 10-25% for females and 5-12% for males. On average, one in five people will experience depression in their lives and about 100,000 adults will live with depression each year in Australia.

Duloxetine is a serotonin and noradrenalin reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder.

6. Comparator

Appropriately, the submission nominated venlafaxine as the main comparator.

7. Clinical Trials

The submission presented two randomised controlled trials comparing 60mg to 120mg duloxetine with 75mg to 225mg venlafaxine as pivotal evidence. The trials were conducted over 8 weeks and the results were pooled.

A meta-analysis was presented as supportive evidence.

The full list of trials forming the basis of the submission is tabulated below.

Pivotal evidence

Trial/First author	Protocol title	Publication citation
HMBU		
Perahia D et al 2006	Comparing Duloxetine and Venlafaxine in the Treatment of Major Depressive Disorder using a Global Benefit-Risk Approach.	New Clinical Drug Evaluation Unit (NCDEU) Conference June 6-9, 2005; Boca Raton, FL.
HMCQ		
Perahia D et al 2005	Comparing Duloxetine and Venlafaxine in the Treatment of Major Depressive Disorder using a Global Benefit-Risk Approach.	New Clinical Drug Evaluation Unit (NCDEU) Conference June 6-9, 2005; Boca Raton, FL.
Perahia D et al	A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder.	Journal of Psychiatric Research. In Press.

Supportive evidence

Trial/First author	Protocol title	Publication citation
Vis et al., 2005	Duloxetine and Venlafaxine-XR in the Treatment of Major Depressive Disorder: a Meta-Analysis of Randomized Clinical Trials.	Annals of Pharmacotherapy. 39(11):1798-807, 2005.

8. Results of Trials

The results of the key trials are summarised in the table below.

Global benefit risk estimates

	GBR	Duloxetine 60 mg daily (N = 318)		Venlafaxine 150 mg daily (N = 330)		p-value
Pooled Period II		Mean	SE	Mean	SE	
	Linear score	–1.418	0.195	–1.079	0.193	0.217
	Log ratio score	–0.811	0.123	*–0.616*	0.117	0.252
	GBR	**Duloxetine 60–120 mg daily (N = 318)**		**Venlafaxine 150–225 mg daily (N = 330)**		**p-value**
Pooled Period II/III		Mean	SE	Mean	SE	
	Linear score	–0.349	0.214	–0.121	0.203	0.440
	Log ratio score	–0.186	0.114	–0.067	0.112	0.456

N is the number of patients with at least one post-baseline $HAMD_{17}$ score. Abbreviation: GBR, global benefit-risk.

The PBAC considered that the primary outcome measure of global benefit-risk (GBR)assessment (Chuang-Stein et al. 1991) which was used in the two presented trials did not provide an optimal basis to assess the non-inferiority of duloxetine and venlafaxine. The GBR is a composite outcome measured on a categorical scale and the GBR-based outcome data are therefore difficult to interpret. The Committee considered that the data provided for mean change from baseline to endpoint in $HAMD_{17}$ scores provided the more appropriate basis upon which to assess the submission's claim of non-inferiority, noting that the $HAMD_{17}$

has been relied on by PBAC in previous assessment of the comparative efficacy of treatments for major depressive disorder.

$HAMD_{17}$ total scores: Change from base line to endpoint: study period II and II/III

Therapy	N	Baseline		Endpoint change		
		Mean	SD	LS mean	SE	p-value
HMBU						
Period II						
Duloxetine 60 mg	159	23.1	3.85	–12.3	0.49	0.763
Venlafaxine150 mg	164	23.1	3.40	–12.3	0.47	
Period II/III						
Duloxetine 60–120 mg	159	23.1	3.85	–14.3	0.51	0.204
Venlafaxine 150–225 mg	164	23.1	3.40	–15.2	0.48	
HMCQ						
Period II						
Duloxetine 60 mg	159	22.3	3.42	–11.2	0.54	0.338
Venlafaxine 150 mg	166	22.3	3.30	–11.9	0.52	
Period II/III						
Duloxetine 60–120 mg	159	22.3	3.42	–15.0	0.55	0.782
Venlafaxine 150–225 mg	166	22.3	3.30	–15.2	0.53	

Abbreviations: SD, standard deviation; LS least square mean; SE, standard error.

There has been concern for the potential of hepatic toxicity due to duloxetine. Hepatotoxicity was not addressed in the submission, but was addressed in the statement of facts and contention for the administrative appeals tribunal. One serious adverse event was reported in the two head to head randomised controlled trials. The type of event was not identified. A significantly greater number of patients discontinued duloxetine treatment (40, 12.1%), compared with venlafaxine (21, 6.2%; p=0.008), due to adverse events.

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

9. Clinical Claim

The submission claimed that duloxetine was no worse than venlafaxine in terms of effectiveness and toxicity. The PBAC did not accept this claim.

10. Economic Analysis

The submission presented a preliminary economic evaluation. The choice of the cost-minimisation approach was considered valid. The resources included were drug costs.

The equi-effective doses in the context of cost-minimisation based on the trial data were estimated by the submission to be duloxetine 60mg to 120mg for duration as necessary and venlafaxine 150mg to 225mg for duration as necessary.

As the PBAC did not accept the submissions clinical claim, the results of the economic analysis were not considered valid.

11. Estimated PBS Usage and Financial Implications

The financial savings/year to the PBS minus any savings in use of other drugs was estimated by the submission to be < $10 million in Year 4. This was considered to be a likely over-estimate as the overall market is not expected to grow, or grow more rapidly, as a result of listing duloxetine.

12. Recommendation and Reasons

The PBAC noted that the pooled results of the two randomised controlled studies comparing duloxetine 60 mg to 120 mg daily with venlafaxine 150 mg to 225 mg daily (following an initial two weeks treatment with 75 mg daily) had failed to demonstrate that duloxetine was non-inferior to venlafaxine using the pre-specified non-inferiority margin for mean change in the $HAMD_{17.}$ The upper bounds of the 1-sided 97.5% confidence intervals for the treatment group difference in mean change in $HAMD_{17}$ between the duloxetine and venlafaxine groups exceeded the non-inferiority margin of 1.15. The PBAC did not accept the sponsor's argument in the pre-PBAC response, that the pre-specified non-inferiority margin may have been overly restrictive resulting in a false negative result.

Although the Committee accepted as plausible the sponsor's argument that the higher discontinuation rate in the duloxetine group might be due to the design of the study in which all duloxetine patients were started on a full therapeutic dose of 60 mg whereas the venlafaxine patients were titrated from a lower dose of 75 mg, thus favouring the venlafaxine group, the PBAC remained concerned that, in the presented trials, discontinuations due to adverse events were approximately double in the duloxetine treated group compared to the venlafaxine group. Furthermore the adverse event data were from a short term trial in relatively young patients (mean age circa 40 years), whereas in clinical practice duloxetine was likely to be used longer term and in older patients and might therefore be associated with additional or more serious toxicity. The submission did not provide any additional safety data that might address this concern.

The PBAC thus rejected the submission because it had failed to demonstrate that duloxetine is non-inferior to the comparator in terms of effectiveness and because of uncertainty about its comparative safety.

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 application was rejected by the PBAC at its meeting in July 2007 on the basis that non-inferiority versus the agreed comparator was not adequately demonstrated.

Eli Lilly acknowledges that further analysis and explanation of the clinical trial findings would be helpful in any future consideration of CYMBALTA® by the PBAC. Expert opinion indicates that patient response to currently available antidepressants is variable and additional antidepressant options are still required.

The sponsor refers to its own website (www.lilly.com.au) for more details.