

PUBLIC SUMMARY DOCUMENT

Product: Duloxetine Hydrochloride, capsules, 30 mg and 60 mg (base), Cymbalta[®]

Sponsor: Eli Lilly Australia Pty Ltd

Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought a restricted benefit listing for treatment of major depressive disorder (MDD).

2. Background

Duloxetine was first considered by the PBAC at its meeting in July 2007. The Committee rejected the submission because it had failed to demonstrate that duloxetine was non-inferior to the comparator, venlafaxine, in terms of effectiveness and because of uncertainty about its comparative safety.

3. Registration Status

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

4. Listing Requested and PBAC's View

Restricted benefit

Major depressive disorders

The PBAC had no objections to the requested wording of the restriction.

5. Clinical Place for the Proposed Therapy

Duloxetine would provide an alternative serotonin-noradrenaline reuptake inhibitor (SNRI) for the treatment of major depressive disorder.

6. Comparator

The submission nominated venlafaxine, also a SNRI, as the main comparator. This was as previously agreed by the PBAC.

7. Clinical Trials

As in the previous submission, two multicentre, randomised, double blind, parallel controlled trials comparing 60-120 mg duloxetine and 75-225 mg venlafaxine over a 12 week period (HMBU and HMBQ) were presented. The trials were designed a priori to be pooled. Non-inferiority assessment and additional analyses of the trial data using a mixed-model repeated measures (MMRM) approach are presented in the re-submission.

Details of the trials presented in the re-submission are shown in the table below.

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, 2008	A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of major depressive disorder.	Journal of Psychiatric Research. 42(1):22-34, Jan 2008

8. Results of Trials

The focus of the re-submission was determining non-inferiority of duloxetine over venlafaxine using overall mean change from baseline to endpoint on HAMD₁₇ (17-item Hamilton Rating Scale for Depression) total scores at 6 and 12 weeks.

The key results are summarised in the tables below.

Mean change in HAMD₁₇ total scores from baseline to endpoint (pooled data):

Population	Duloxetine Mean (SD)				Venlafaxine Mean (SD)			
	N	Baseline	Endpoint	Change	N	Baseline	Endpoint	Change
Study Period II (weeks 1-6)								
ITT	318	22.70 (3.66)	11.94 (7.23)	-10.76 (6.99)	330	22.69 (3.37)	11.20 (6.78)	-11.49 (6.53)
PP	244	22.71 (3.68)	10.94 (6.96)	-11.77 (6.49)	272	22.71 (3.42)	10.47 (6.54)	-12.24 (6.25)
Study Period II/III (weeks 1-12)								
ITT	318	22.70 (3.66)	10.08 (7.64)	-12.62 (7.62)	330	22.69 (3.37)	9.10 (7.01)	-13.58 (6.75)
PP	231	22.74 (3.72)	8.54 (7.06)	-14.21 (6.81)	250	22.65 (3.41)	7.90 (6.44)	-14.76 (6.18)

Abbreviations: HAMD₁₇: 17-item Hamilton Rating Scale for Depression; ITT: intent-to-treat; PP: per-protocol.

Difference of Least Squares Mean change (Duloxetine-Venlafaxine) in HAMD₁₇ Total Score for Study Period II and II/III (pooled data):

Method	Population	LS Mean Difference (95%CI)	P-value from 1-sided 97.5% CI for non-inferiority
LOCF II	ITT	0.74 (-0.24, 1.72)	0.2061
	PP	0.51 (-0.54, 1.55)	0.1139
LOCF II/III	ITT	0.79 (-0.33, 1.91)	0.2643
	PP	0.66 (-0.45, 1.77)	0.1935
MMRM II	ITT	0.04 (-0.70, 0.77)	0.0014
	PP	0.15 (-0.66, 0.96)	0.0078
MMRM II/III	ITT	0.12 (-0.62, 0.86)	0.0031
	PP	0.24 (-0.57, 1.05)	0.0141

Abbreviations: HAMD₁₇: 17-item Hamilton Rating Scale for Depression; LOCF: Last Observation Carried Forward (ANCOVA analysis); MMRM:- mixed-model repeated measures; ITT: intent-to-treat; PP:- per-protocol.

In the July 2007 submission, an ANCOVA last observation carried forward (LOCF) analysis was used to compare mean change in HAMD₁₇ total scores from baseline to endpoint in the two treatment groups. The re-submission stated that the results of the ANCOVA LOCF analyses are inconclusive in determining non-inferiority of duloxetine over venlafaxine. This is because the LOCF approach underestimates differences which would produce a result that is less conservative in a non-inferiority test. However, the re-submission claimed that using the MMRM overall mean estimate clearly demonstrates that duloxetine is non-inferior compared to venlafaxine on the HAMD₁₇ total score, as the upper bound of the 97.5% one-sided CI meets the pre-specified non-inferiority margin of 1.15 in all study periods and populations analysed.

The MMRM approach was accepted by the PBAC as providing a more valid estimate of the true difference between duloxetine and venlafaxine compared with the last observation carried forward (LOCF) values, because the outcome values from all time points are used.

Serious adverse events were reported in five (1.5%) venlafaxine-treated patients compared with one (0.3%) duloxetine-treated patient.

The most frequently reported treatment-emergent adverse events in both treatment groups were nausea, headache, dry mouth, constipation, excessive sweating, and dizziness. Statistically significantly more duloxetine patients reported incidences of nausea (43.6% vs. 35.0%) and dizziness (16.1% vs. 10.4%) in study period II (first 6 weeks of treatment). The maximum reported severity of nausea was statistically significantly higher with duloxetine (mild, 18%; moderate, 20%; severe, 6.1%) compared with venlafaxine (mild, 20%; moderate, 13%; severe, 2.7%; p=0.022).

The re-submission also presented new toxicity data. There was no evidence presented to suggest that duloxetine treatment has clinically relevant effects on heart rate, blood pressure or ECG profiles in the patients who participated in the clinical trials. There were no data presented to suggest an increased risk of hepatic toxicity when taking duloxetine. The re-submission stated that duloxetine is well tolerated in long-term use, and has a similar toxicity profile in elderly patients with major depressive disorders (MDD) as in the general population of patients with MDD.

9. Clinical Claim

The re-submission described duloxetine as non-inferior in terms of comparative effectiveness over venlafaxine. It stated that there was a higher incidence of treatment emergent adverse events associated with duloxetine in the initial period of treatment, however this reduced with ongoing treatment. The PBAC considered this claim reasonable.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as duloxetine 60 mg to 120 mg per day for duration as necessary and venlafaxine 150 mg to 225 mg for duration as necessary.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be over 200,000 in Year 5, and financial savings per year to the PBS to be between \$10-30 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of duloxetine on the PBS for major depressive disorders on a cost-minimisation basis compared with venlafaxine and that the equi-effective doses are duloxetine 60 mg and venlafaxine 150 mg, noting that the submission's lower proposed price for the 60 mg capsule is acceptable.

The PBAC considered the claim that duloxetine was non-inferior to venlafaxine with a higher incidence of treatment emergent adverse effects as reasonable.

The PBAC considered that the 30 mg capsules should have no repeats as the 30 mg dosage is mainly used for titration purposes and therefore repeats cannot be justified. No evidence was presented that indicated the 30 mg dose had efficacy in addition to the use for titration.

Recommendation

DULOXETINE HYDROCHLORIDE, capsules, 30 mg and 60 mg (base)

Restriction: Restricted benefit
Major depressive disorders.

Maximum quantity: 28 (30 mg and 60 mg)

Repeats: Nil (30 mg)

5 (60 mg)

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 notes and appreciates the PBAC's acceptance of the MMRM analysis as being more appropriate to determine the relative effectiveness of duloxetine compared with venlafaxine.