

PUBLIC SUMMARY DOCUMENT

Product: Escitalopram, tablet 10 mg (base), tablet 20 mg (base), oral solution 10 mg (base) per mL, Lexapro[®]

Sponsor: Lundbeck Australia Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

To seek an extension to the listing of escitalopram to include social anxiety disorder (social phobia) (SAD) and generalised anxiety disorder (GAD).

2. Background

Escitalopram was originally considered by the PBAC at its September 2003 meeting. The PBAC recommended listing on a cost-minimisation basis with citalopram for the treatment of major depressive disorders, with escitalopram 10 mg being equivalent to citalopram 20 mg and escitalopram 20 mg being equivalent to citalopram 40 mg. Escitalopram was listed as a PBS item on 1 February 2004.

3. Registration Status

The TGA-registered indication for escitalopram was extended on 19 September 2005 to include “the treatment of Social Anxiety Disorder (Social Phobia), and for the treatment of Generalised Anxiety Disorder in adults”.

4. Listing Requested and PBAC’s View

Restricted benefit

Social anxiety disorder (social phobia);
Generalised anxiety disorder.

- Tablet 10 mg (base); tablet 20 mg (base)

Special Pharmaceutical Benefits

Restricted benefit

Social anxiety disorder (social phobia);
Generalised anxiety disorder.

- Oral solution 10 mg (base) per mL

See Recommendation and Reasons for the PBAC’s view

5. Clinical Place for the Proposed Therapy

A treatment for social and generalised anxiety disorders.

6. Comparator

The submission nominated paroxetine as the comparator. There are currently no therapies on the PBS for SAD or GAD. Paroxetine has TGA approval for SAD/GAD and was considered by the submission to be the most commonly prescribed treatment for both indications in general practice. Sertraline (SAD) and venlafaxine (SAD and GAD) are also TGA-approved and could also be comparators.

See Recommendations and Reasons for the PBAC's view.

7. Clinical Trials

Social Anxiety Disorder (SAD): A single randomised trial comparing fixed doses of escitalopram (5, 10 and 20 mg/day), paroxetine (20 mg/day) and placebo in adult patients with SAD over 24 weeks.

Generalised Anxiety Disorder (GAD): The basis of the submission was a meta-analysis of two randomised trials, one flexible dose, direct (head to head), comparison of escitalopram (10-20 mg) and paroxetine (20-50 mg/day) in adult patients with GAD over 24 weeks, and one trial comparing fixed doses of escitalopram (5, 10 and 20 mg/d), paroxetine (20 mg/d) and placebo in adult patients with GAD over 12 weeks.

The trials have been published at the time of submission as follows:

First author	Protocol title	Publication citation
Lader et al (2004) (Trial 99570)	Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised double-blind, placebo-controlled, fixed-dose study.	Depression and anxiety 2004; 19:241-8.
Bielski et al (2005) (Trial SCT-MD-10)	A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalised anxiety disorder.	Annals of Clinical Psychiatry 2005; 17(2):65-9
Baldwin DS et al (2006) (Trial 99815)	Escitalopram and paroxetine in the treatment of generalised anxiety disorder.	British Journal of Psychiatry 2006, 189:264-272.

The PBAC noted, that although the product information stated that long term treatment is necessary, the duration of the trials was relatively short (12-24 weeks).

8. Results of Trials

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

SAD: CONFIDENCE INTERVALS FOR DIFFERENCES IN CLINICAL EFFICACY (ESCITALOPRAM 5 MG, 10 AND 20 MG VS PAROXETINE 20 MG (WEEK 24): TRIAL 99270

	ESC 5 vs PAR 20		ESC 10 vs PAR 20		ESC 20 vs PAR 20	
	Estimate	95%CI	Estimate	95%CI	Estimate	95%CI
LSAS total score	1.80	-3.96, 7.56	2.19	-3.73, 8.12	-7.68	-13.43, -1.93
LSAS fear & anxiety	1.07	-1.88, 4.03	1.23	-1.82, 4.28	-3.76	-6.72, -0.81
LSAS avoidance	0.55	-2.47, 3.57	1.03	-2.10, 4.15	-4.10	-7.12, -1.08
CGI-S	0.12	-0.16, 0.41	0.07	-0.22, 0.36	-0.35	-0.63, -0.07
CGI-I	0.00	-0.21, 0.22	0.04	-0.18, 0.26	-0.29	-0.51, -0.08

PBO = placebo; PAR = paroxetine; ESC=escitalopram; LSAS = Liebowitz Social Anxiety Scale; CGI-S = Global Clinical Impression Severity Scale; CGI-I = Global Clinical Impression Improvement Scale

The 95% confidence intervals fall within the post-hoc specified range of -10 to +10 on the LSAS total score (primary efficacy endpoint). Based on these results, the submission claimed that escitalopram 5 mg and 10 mg were of equivalent efficacy to paroxetine 20 mg. Escitalopram 20 mg was claimed to be superior to paroxetine 20mg. However, the PBAC noted the post-hoc measure of equivalence was considered invalid. Trial 99270 was designed and statistically powered to test the superiority of escitalopram versus placebo in the total LSAS score at week 12 (LOCF). The trial was not designed to estimate equivalence (or non-inferiority). The paroxetine trial arm was included in its lowest recommended dose as an active control.

GAD: Results of meta-analysis of studies SCT-MD-20 and 99815 a

A meta-analysis was conducted including trial SCT-MD-20 and a subset of patients from trial 99815 who received escitalopram 10 mg/d and paroxetine 20 mg/d. The results of the meta-analysis are shown in the following table.

Parameter	Difference escitalopram vs paroxetine (95% CI)			
	Week 12	p-value	End of study ^b	p-value
- HAMA total score	2.12 (0.68, 3.56)	0.0040	2.08 (0.62, 3.55)	0.0054
- CGI-S	0.28 (0.06, 0.49)	0.0131	0.31 (0.08, 0.54)	0.0074
- CGI-I	0.33 (0.13, 0.54)	0.0016	0.33 (0.12, 0.55)	0.0024
Responders %				
- Paroxetine	59.9	0.0201	60.9	0.0092
- Escitalopram	70.6		72.7	

HAMA=Hamilton Anxiety Scale, CGI-S = Global Clinical Impression Severity Scale; CGI-I = Global Clinical Impression Improvement Scale

a: Includes all patients from study SCT-MD-20 and patients treated with paroxetine and escitalopram 10 mg from study 99815

b: Week 24 for study SCT-MD-20 and week 12 for study 99815

The submission claimed the results show that escitalopram was superior to paroxetine for the treatment of GAD. The PBAC was advised it was not valid to claim superiority with the meta-analytic method and results presented.

The PBAC noted that there was only limited discussion in the submission about what might constitute a clinically important change on the LSAS and HAMA scales. The submission stated that a 10 point difference on the LSAS scale was likely to be clinically significant, but did not provide any further evidence to support this statement.

9. Clinical Claim

The submission claimed escitalopram was no worse than paroxetine in terms of effectiveness or toxicity. On balance the PBAC accepted escitalopram and paroxetine are likely to be of similar efficacy and safety on the basis of dose relationship of 1:2, although the clinical importance of the results achieved by either drug remains unresolved.

10. Economic Analysis

A preliminary economic evaluation was presented. The choice of the cost-minimisation approach was valid. The resources included were drug costs of the mean daily doses of escitalopram and paroxetine from trial SCT-MD-20.

See Recommendations and Reasons for PBAC's view.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial cost per year to the PBAC would be less than \$10 million.

12. Recommendation and Reasons

The PBAC acknowledged that, in the most severe forms, these conditions are debilitating and serious but agreed that in view of the potential overuse of these drugs, the following should be added to the restriction:

- restricted to allow use only after non-pharmacological methods have failed;
- entry criteria for the trials should be included as part of the listing, including a minimum LSAS score; and
- restricted to patients over 18 years of age.

The sponsor accepted this advice and had proposed that patients should meet the DSM-IV criteria for these conditions to qualify for treatment under the PBS.

The PBAC noted that there are currently no therapies on the PBS for SAD or GAD. Paroxetine has TGA approval for SAD/GAD and is considered by the submission to be the most commonly prescribed treatment for both indications in general practice. Sertraline (SAD) and venlafaxine (SAD and GAD) are also TGA-approved and could also be comparators. Given that the first line treatments of anxiety disorder are non-pharmacological (such as cognitive behavioural therapy), the choice of paroxetine as a subsequent line of therapy is probably reasonable as an appropriate comparator according to the 2006 PBAC Guidelines as the therapy likely to be replaced in practice. However, as the cost-effectiveness of paroxetine is unknown in SAD or GAD, the comparison did not provide PBAC with a basis for a recommendation to list escitalopram because the cost-minimisation approach taken by the submission was not sufficiently informative. Although it is acknowledged that paroxetine is probably used to treat these conditions and thus might form a useful frame of reference, a comparison would need to be made with standard medical management to better inform the PBAC about the cost effectiveness of both paroxetine and escitalopram.

It was noted that, although the product information states that long term treatment is necessary, the duration of the trials was relatively short (12-24 weeks). The trial in SAD was also of only 24 weeks in duration and the PBAC thus considered that there was uncertainty about the long-term effectiveness of escitalopram in anxiety disorders.

The submission stated that a 10-point difference on the LSAS scale is likely to be clinically important, but did not provide any further evidence to support this statement. In the absence of definitive information about what a clinically important difference might be, it is not possible to confirm non-inferiority. The PBAC considered that this was a critical issue to enable resolution of whether or not the differences in the subjective scores can be extrapolated to clinical outcomes. The PBAC also noted that placebo also produced a 10-point improvement in the LSAS scores. The PBAC was of the opinion that the claim of equivalence for SAD is based on weak evidence. On the basis of a dose relativity of 1:2, the difference between escitalopram and paroxetine is small and the upper limit of the confidence interval is within a range of +/- 10 points in the LSAS score.

The fixed dose trial regimen in presented trials does not reflect dose titration of the drug or comparator likely to occur in clinical practice. In addition, paroxetine is included in the fixed dose trials at the lowest recommended dose. The dose titration study, which best reflects clinical practice showed no difference between the two drugs in the management of GAD with a dose relativity of 1:2, although the clinical importance of the results achieved by either drug remains uncertain.

The PBAC also agreed that SAD and GAD are associated with significant psychiatric co-morbidity (major depression, panic disorder, specific phobia and post traumatic stress disorder) that may necessitate a change in optimal pharmacological management. Conversely, overlapping symptoms between discrete indications may narrow treatment options. These issues were not adequately addressed in the submission.

However, on balance, the PBAC accepted that escitalopram and paroxetine are likely to be of similar efficacy and safety on the basis of a dose relativity of 1:2. However, the issue of the cost-effectiveness of either of these products remained unresolved.

The PBAC thus rejected the submission because of uncertain cost-effectiveness.

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

Lundbeck is disappointed with the outcome and we are working with the PBAC to resolve the issues and gain PBS listing of escitalopram for social and generalized anxiety disorders.