PUBLIC SUMMARY DOCUMENT
Product: Escitalopram oxalate, tablets, 10 mg and 20 mg (base), Lexapro®
Sponsor: Lundbeck Australia Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

To seek an extension to the restricted benefit listing of escitalopram to include social anxiety disorder (social phobia; SAD).

2. Background

At the September 2003 meeting, the PBAC recommended listing escitalopram 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.

At the March 2007 meeting, the PBAC rejected a combined submission seeking an extension to the listing of escitalopram to include social anxiety disorder (social phobia) and generalised anxiety disorder because of uncertain cost-effectiveness. The PBAC acknowledged that, in the most severe forms, these conditions are debilitating and serious but considered there is potential for overuse of these drugs.

3. Registration Status

Escitalopram was registered by the TGA on 16 September 2003 and is indicated for:

- Treatment of major depression.
- Treatment of social anxiety disorder (social phobia).
- Treatment of generalised anxiety disorder.
- Treatment of obsessive-compulsive disorder.

The TGA registered indications were extended to include treatment of social anxiety disorder on 19 September 2005.

4. Listing Requested and PBAC's View

Restricted benefit

For the treatment of moderate to severe social anxiety disorder (social phobia; SAD), as defined by DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition).

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Individuals with Social Phobia experience concerns about many or most social situations, especially those involving social interaction. They almost always experience symptoms of anxiety (e.g. palpitations, tremors, sweating, diarrhoea, muscle tension, blushing, and confusion) and in severe cases, these symptoms may meet the criteria for a Panic Attack. They recognise that the fear is excessive or unreasonable but will typically avoid feared situations.

Escitalopram would provide a treatment option for social anxiety disorder.

6. Comparator

The re-submission nominated placebo as the main comparator. This was accepted by the PBAC as appropriate.

7. Clinical Trials

The re-submission presented three studies comparing escitalopram and placebo. All studies were double-blind, randomised, controlled, multicentre, parallel-group direct comparisons. The re-submission also provided a meta-analysis for studies 99012 and 99270.

Details of the trials published at the time of submission are shown in the table below.

Trial ID	Protocol title/ Publication title	Publication citation
99270 Lader M	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(4):241-248.
99012 Kasper S	Escitalopram in the treatment of social anxiety disorder: Randomised, placebo-controlled, flexible-dosage study.	British Journal of Psychiatry 2005; 186(MAR.):222-226.
99269 Montgomery SA	A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder.	Journal of Clinical Psychiatry 2005; 66(10):1270-1278.

The PBAC noted a Consumer Report on the impact of social anxiety disorders and phobias on daily living.

8. Results of Trials

The primary outcome of trials 99270 and 99012 was the difference in the mean improvement from baseline to study endpoint in the Leibowitz Social Anxiety Scale (LSAS) Total Score. This was a key secondary outcome in relapse prevention Study 99269. An improvement of at least 10 points on the LSAS has been suggested as showing a clinically relevant improvement. The key results are summarised in the table below.

Results of primary outcome: (adjusted mean change in LSAS total score, LOCF) -Escitalopram versus placebo

	99270		99012	99269
	ESC 10mg	**ESC 20mg**	**Escitalopram**	**Escitalopram**
Week 12	-5.07 (-10.32, 0.18)	**-10.31** **(-15.56, -5.06)**	**-7.29** **(-12.37, -2.21)**	-10.97 (-14.70, -7.25)
Week 24	-7.45 (-13.29, -1.62)	-15.09 (-20.92, -9.25)		-12.82 (-16.95, - 8.70)
Meta analysis (Week 12) (99270 & 99012) Using unadjusted change data		**-8.74 (-12.60, -4.89)**		

The mean change in LSAS total score for escitalopram 10 mg was -5.07 (at week 12) and -7.45 (at week 24), and for escitalopram 20 mg was -10.31(at week 12) and -15.09 (at week 24) for study 99270, -7.29 for study 99012 and -10.97 (at week 12) and -12.82 (at week 24) for study 99269.

The PBAC noted that although the meta-analysis of the primary outcome, adjusted mean change in LSAS mean score, (meta-analysis of studies 99270 & 99012, mean change -8.74 (95% CI -12.60, -4.89) did not meet the clinically significant difference of 10 points at week 12, secondary outcomes at the 24 week time point showed a significantly greater response to therapy (based on significant improvements in the percentage of patients with a $\geq$50% reduction in LSAS, Clinical Global Impression - Improvement (CGI-I) scores, and Clinical Global Impression – Severity (CGI-S) scores).

The results of the relapse prevention study 99269 showed twice as many patients in the placebo group relapsed as compared to escitalopram.

Results of primary outcome: Analysis of time to relapse (Study 99269)

Treatment	n / N (%)	No. of relapses	% Relapsed	Mean survival days
Escitalopram	190/190 (100)	42	22.1	135.3
Placebo	181/182 (99.5)	91	50.3	103.5

The re-submission presented new toxicity data. The re-submission stated that the comparative safety of escitalopram is similar/non-inferior to placebo. The key results are summarised in the table below.

Summary results of secondary safety outcomes for meta-analysis

Outcome – meta-analyses *	Escitalopram n / N	Placebo n / N	Relative Risk (95%CI)
Total withdrawals	75/351	71/343	1.03 (0.77, 1.37)
Withdrawals - lack of efficacy	13/351	31/343	0.41 (0.22, 0.77)
Withdrawals – adverse events	34/351	16/343	**2.08 (1.17, 3.69)**
Treatment emergent Adverse events	266/351	192/343	**1.35 (1.21, 1.51)**

* 99270 and 99012

The meta-analysis results for Studies 99270 and 99012 showed more withdrawals due to adverse events and treatment emergent adverse events in the escitalopram arm compared with placebo.

The PBAC accepted escitalopram to be reasonably well tolerated with a higher adverse event withdrawal rate than placebo.

9. Clinical Claim

The re-submission claimed that escitalopram was superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo.

See Recommendations and Reasons for PBAC's view.

10. Economic Analysis

A modelled economic evaluation was presented. The PBAC considered this approach was appropriate. The economic model was a decision tree, with an appropriate structure. Health outcomes were based on state- or treatment-specific utilities and the amount of time spent in the state or treatment. Costs were based on resource use, drugs and GP and specialist visits, but the main driver of the costs in the model are number of visits.

The re-submission estimated the incremental cost per extra Quality-Adjusted Life-Year (QALY) gained to be less than $15,000.

The PBAC noted a number of criticisms of the economic model. However, the PBAC considered that irrespective of some of the identified issues with the model, the cost of the intervention is reasonable value for money in the context, and while the incremental cost-effectiveness ratio (ICER) predicted by the model may not be accurate, the sensitivity analyses indicated a high probability that the ICER would be acceptable.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated the expected number of escitalopram patients per year to be between 10,000 and 50,000 in Year 5. The net cost to the PBS was estimated to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of escitalopram for the treatment of moderate to severe social anxiety disorder (SAD) at the benchmark price based on an acceptable cost-effectiveness ratio compared to placebo.

The PBAC noted that although the meta-analysis of the primary outcome, adjusted mean change in LSAS mean score, (meta-analysis of studies 99270 & 99012, mean change -8.74 (95% CI -12.60, -4.89) did not meet the clinically significant difference of 10 points at week 12, secondary outcomes at the 24 week time point showed a significantly greater response to therapy (based on significant improvements in the percentage of patients with a $\geq$50% reduction in LSAS, CGI-I scores, % patients with CGI-I$\leq$2 and CGI-S scores).

During the hearing, the PBAC was advised the clinical place of escitalopram was in the treatment of the more severe patient in whom non-pharmacological methods had not been successful. Further, that treatment benefit was usually seen at 4 months and with the 20 mg dose.

The PBAC noted that cognitive behavioural therapy (CBT) is now funded under the Medicare Benefits Scheme and the management of SAD could be included in General Practitioner Mental Health Care Plans offering a more structured approach to care than previously. The PBAC recommended that the restriction for escitalopram should be limited to the setting of these Plans or to psychiatrist prescribers.

The PBAC therefore considered that availability of escitalopram should be limited to the severe or moderately severe patient in whom non-pharmacological treatment had failed. However, "non-pharmacological treatment" need not be a formal external psychological intervention and could be provided by the prescriber.

The PBAC noted a number of criticisms of the economic model. However, the PBAC considered that irrespective of some of the identified issues with the model, the cost of the intervention is reasonable value for money in the context and while it may not be cost saving as predicted by the model, the sensitivity analyses indicated a high probability that the ICER would be acceptable.

The PBAC requested that the National Prescribing Service undertake major work on the indications of GAD and SAD.

Recommendation

ESCITALOPRAM OXALATE, tablets, 10 mg (base) and 20 mg (base).
Extend listing to include:

Restriction:	Restricted benefit Moderate to severe social anxiety disorder (social phobia; SAD), as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, in a patient who has not responded to non-pharmacological therapy and for whom: (a) a GP Mental Health Care Plan, as described under item 2710 of the Medicare Benefits Schedule, has been prepared; or (b) who has been assessed by a psychiatrist. Restricted benefit Continuing PBS subsidised treatment, for moderate to severe social anxiety disorder (social phobia; SAD), of a patient commenced on escitalopram prior to 1 March 2008.
Maximum quantity:	28
Repeats:	5

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 Australia welcomes the PBAC's decision to recommend Lexapro for listing on the PBS for the treatment of Social Anxiety Disorder (Social Phobia).