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 generalised anxiety disorder (GAD).

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 generalised anxiety disorder on 19 September 2005.

4. Listing Requested and PBAC's View

Restricted benefit

For the treatment of moderate to severe generalised anxiety disorder (GAD), 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

Generalised anxiety disorder (GAD) is characterised by chronic and uncontrollable worrying and somatic anxiety such as tension, hypervigilance and insomnia. The sufferer knows the worry is excessive or unrealistic but feels unable to control it. GAD is associated with other psychiatric disorders.

Escitalopram would provide an alternative treatment option for generalised anxiety disorders.

6. Comparator

The re-submission nominated benzodiazepines, particularly diazepam and oxazepam, and placebo as the main comparators. This was as previously advised by the PBAC.

7. Clinical Trials

An indirect comparison between escitalopram and benzodiazepines, using placebo as a common comparator, was undertaken.

The re-submission presented six studies comparing escitalopram and placebo, and one study comparing diazepam and placebo. All studies were double-blind, randomised, controlled, multicentre, parallel-group direct comparisons. The re-submission also presented one supportive, non-randomised, open-label extension study of the safety and efficacy of escitalopram in GAD.

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

Trial/First Author	Publication title	Citation
Escitalopram		
SCT-MD-07 Davidson JRT et al.	Escitalopram in the treatment of generalised anxiety disorder: Double-blind, placebo controlled, flexible-dose study.	Depression and Anxiety 2004; 19(4):234-240.
99815 Baldwin DS et al.	Escitalopram and Paroxetine in the treatment of generalized anxiety disorder (GAD).	British Journal of Psychiatry 2006; 189:264-272.
99769 Allgulander C	Prevention of relapse in generalized anxiety disorder by escitalopram treatment.	International Journal of Neuropsychopharmacology 2006;9(5):495-505.
SCT-MD-17(MD-17) Davidson JRT	Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder	Journal of Clinical Psychiatry 2005;66(11):1441-14465.
Benzodiazepine		
Hackett et al.	A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder.	European Psychiatry, 2003. 18(4): 182-187.

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

8. Results of Trials

The primary outcome of the trials was the difference in the mean improvement from baseline to study endpoint in the Hamilton Anxiety Scale (HAM-A) Total Score. The HAM-A is considered the gold standard scale for measuring the severity of illness in patients with GAD.

The PBAC agreed that the clinical trial data presented demonstrate small, but statistically significant, differences between escitalopram and placebo (1-3 points, meta-analysis 2 points) in the HAM-A score.

A summary of the meta-analyses of secondary outcomes (psychic symptoms – anxious mood, psychic tension) at eight weeks was presented. The PBAC noted that there were significantly

improved outcomes in all key secondary efficacy outcomes at 8 weeks, favouring escitalopram.

The following table shows the results of relapse prevention study.

Summary of results relapse prevention study

Trial (Mean dose)	Rx	n/N (%)	Baseline (SD)	Time 1 (SD)	Time 2 (SD)	Mean change T1 (SD)	Mean change T2 (SD)	Diff Esc-Pbo (95%CI) P value
Escitalopram 99769 relapse prevention study								
Open label phase [c]	Esc	187	27.26 (4.15)	8.37 (5.63)	5.74 (3.06)	-18.88 (7.16)	-21.51 (5.51)	NR
	Pbo	188	27.08 (4.69)	7.67 (4.77)	5.07 (3.15)	-19.41 (6.55)	-22.01 (5.96)	
	NonR	116	27.72 (4.39)	18.56 (9.09)	18.94 (9.24)	-9.16 (8.97)	-8.78 (9.17)	
Randomised phase [d]	Esc	186/187 (99)	5.67 (2.88)	7.78 (6.47)	7.80 (7.31)	2.12 (6.54)	2.13 (7.46)	T1 -5.96 (-7.54, -4.38) p<0.001
	Pbo	187/188 (99)	5.02 (3.07)	13.10 (8.72)	13.76 (8.98)	8.08 (8.90)	8.74 (8.95)	T2 -6.61 (-8.28, -4.94) p<0.001

Notes: c: In the open label phase the three treatment groups are: Esc = open label phase responders later randomised to esc; Pbo=open label responders later randomised to placebo; NonR=Non-responders in open label phase.

d: 99769 - baseline for double blind phase, difference esc vs placebo was calculated by the re-submission as statistical analyses were not conducted for secondary outcomes.

NR=not reported; SD standard deviation.

In the relapse study (99769), time to relapse was the primary outcome and HAM-A total score was a secondary outcome. Patients received 12 weeks of open-label therapy prior to randomisation to escitalopram or placebo. A significant placebo response was observed in the first 12 week open label period. At the end of 12 weeks, responders (HAM-A<10) were randomly assigned to active drug or placebo for a minimum of 24 weeks additional treatment. In this phase the HAM-A score in the placebo arm changed significantly (from a mean of 5 to 13.8) indicating a worsening of the condition but the HAM-A score in the active arm only changed from 5.7 to 7.8. Similarly, the relapse rate was 19% in the escitalopram arm and 56% rate in the placebo arm, a difference which was statistically significant (Chi-squared test, p<0.001) in favour of escitalopram.

The re-submission presented new toxicity data. In the escitalopram studies, there was no difference in total withdrawals and withdrawals due to efficacy but there were more withdrawals due to adverse events in the escitalopram arm compared with placebo arm. There were no differences in the diazepam study.

9. Clinical Claim

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

See Recommendation and Reasons for PBAC's view.

10. Economic Analysis

The re-submission presented a modelled economic evaluation. The PBAC considered that this was appropriate.

The incremental cost per Quality-Adjusted Life-Year (QALY) gained was estimated in the re-submission to be less than $15,000. The PBAC was advised of a number of uncertainties with the economic model.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated the likely number of patients per year treated with escitalopram to be between 10,000 and 50,000 in Year 5 at a net cost per year to the PBS of 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 generalised anxiety disorder (GAD) at the benchmark price based on an acceptable cost-effectiveness ratio compared to placebo.

The PBAC agreed that the clinical trial data presented demonstrate small, but statistically significant, differences between escitalopram and placebo (1-3 points, meta-analysis 2 points) in the HAM-A score. The PBAC noted the argument that other secondary outcomes were also clinically meaningful. The PBAC further agreed that the significant difference in HAM-A would extrapolate to patient relevant outcomes.

The Committee also noted that in the summary of the meta-analyses of secondary outcomes at eight weeks (trial 99815 was at 12 weeks) there were significantly improved outcomes in all key secondary efficacy outcomes, favouring escitalopram.

In the relapse study (99769), time to relapse was the primary outcome and HAM-A total score was a secondary outcome. Patients received 12 weeks of open-label therapy prior to randomisation to escitalopram or placebo. A significant placebo response was observed in the first 12 week open label period. At the end of 12 weeks, responders (HAM-A<10) were randomly assigned to active drug or placebo for a minimum of 24 weeks additional treatment. In this phase the HAM-A score in the placebo arm changed significantly (from a mean of 5 to 13.8) indicating a worsening of the condition but the HAM-A score in the active arm only changed from 5.7 to 7.8. Similarly, the relapse rate was 19% in the escitalopram arm and 56% rate in the placebo arm, a difference which was statistically significant (Chi-squared test, $p<0.001$) in favour of escitalopram.

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. Patient improvement was expected by 4 months, and duration of treatment could be up to 12 months during which time other co-morbidities (depression, alcohol and drug abuse) could be addressed.

The PBAC noted that cognitive behavioural therapy (CBT) is now funded under the Medicare Benefits Scheme and the management of GAD 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 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 recommended that the restriction for escitalopram should include an acceptable severity scale and score threshold capable of accurately determining moderate to severe GAD.

The PBAC noted a number of uncertainties in the model, however, notwithstanding the issues the PBAC accepted that the use of this drug in severe GAD would yield a relatively low ICER and could be cost saving if the outcomes on costs i.e. medical visits are realised.

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 generalised anxiety disorder (GAD), 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 generalised anxiety disorder (GAD), 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 Generalised Anxiety Disorder.