PUBLIC SUMMARY DOCUMENT
Product: Quetiapine fumarate, tablets, 25 mg, 100 mg, 200 mg, 300 mg (base), Seroquel®
Sponsor: AstraZeneca Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application

To submission sought an extension to the current Authority required (Streamlined) listing for immediate release quetiapine to include treatment of a patient with depressive episodes associated with bipolar disorder.

2. Background

The requested indication had not previously been considered by the PBAC.

At the June 2000 meeting, the PBAC recommended an authority required listing for immediate release quetiapine for the treatment of schizophrenia on a cost-minimisation basis compared with risperidone.

At the July 2007 meeting, the PBAC recommended extending the authority required PBS listing for quetiapine immediate release to include the treatment, as monotherapy, for up to 6 months, of an episode of acute mania associated with bipolar I disorder. Listing was effective 1 December 2007.

3. Registration Status

Immediate release quetiapine is TGA registered for use in bipolar disorder as:

- Maintenance treatment of bipolar I disorder, as monotherapy or in combination with lithium or sodium valproate, for the prevention of relapse/recurrence of manic, depressive or mixed episodes.
- Treatment of depressive episodes associated with bipolar disorder.
- Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Depressive episodes associated with bipolar disorder.

For PBAC views see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Bipolar disorders are characterised by episodic depressions and elevations of mood.

Quetiapine would provide an alternative therapy for acute depressive episodes.

6. Comparator

The submission nominated olanzapine as the main comparator.

The PBAC considered that olanazapine was not the appropriate comparator as olanzapine is not TGA registered or PBS listed for acute treatment of depressive episodes in bipolar disorder.

For PBAC's view see Recommendations and Reasons.

7. Clinical Trials

The scientific basis of the submission was an indirect comparison of quetiapine versus olanzapine using placebo as a common comparator. The submission presented four (4) randomised trials comparing quetiapine 300 mg daily and 600 mg daily (fixed dose) BOLDER I and II, EMBOLDEN I and EMBOLDEN II with placebo and one trial of olanzapine (flexible dosing) Tohen et al 2003,versus placebo in patients with bipolar depression. Although the quetiapine trials enrolled patients with both bipolar I and bipolar II disorders, only results of efficacy and safety in the subgroup of patients with bipolar I disorder with acute depressive episodes were indirectly compared between olanzapine and quetiapine. This was because only bipolar I patients were enrolled in the olanzapine trial.

The studies that had been published at the time of the submission, are as follows:

Trial/First author	Protocol title/publication citation	Publication citation
Common reference: placebo		
Quetiapine		
BOLDER I		
Calabrese et al	A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression.	American Journal of Psychiatry 162:1351-1360, 2005.
Hirschfeld et al	Quetiapine in the treatment of anxiety in patients with bipolar I or II depression: A secondary analysis from a randomized, double-blind, placebo-controlled study.	Journal of Clinical Psychiatry 67:355-362, 2006.
Cookson et al	Number needed to treat and time to response/remission for quetiapine monotherapy efficacy in acute bipolar depression: Evidence from a large, randomized, placebo-controlled study.	International Clinical Psychopharmacology 22:93-100, 2007.
Endicott et al	A randomized, double-blind, placebo-controlled study of quetiapine in the treatment of bipolar I and II depression: Improvements in quality of life.	International Clinical Psychopharmacology 22:29-37, 2007.
Vieta E et al	Quetiapine monotherapy in the treatment of patients with bipolar I or II depression and a rapid-cycling disease course: A randomized, double-blind, placebo-controlled study.	Bipolar Disorders 9:413-425, 2007.
Gajwani et al	Update on quetiapine in the treatment of bipolar disorder: Results from the BOLDER studies.	Neuropsychiatric Disease and Treatment 3:847-853, 2007.
Weisler et al	Efficacy of quetiapine monotherapy for the treatment of depressive episodes in bipolar I disorder: A post hoc analysis of combined results from 2 double-blind, randomized, placebo-controlled studies. [note: combined analysis with BOLDER II]	Journal of Clinical Psychiatry 69:769-782, 2008.
BOLDER II		
Thase et al 2006	Efficacy of quetiapine monotherapy in bipolar I and II depression: A double-blind, placebo-controlled study (the BOLDER II study).	Journal of Clinical Psychopharmacology 26:600-609, 2006.
Gajwani et al 2007	Update on quetiapine in the treatment of bipolar disorder: Results from the BOLDER studies.	Neuropsychiatric Disease and Treatment 3:847-853, 2007.
Gajwani 2007	BOLDER II study of quetiapine therapy for bipolar depression.	Future Neurology 2:373-377, 2007.

Weisler et al	Efficacy of quetiapine monotherapy for the treatment of depressive episodes in bipolar I disorder: A post hoc analysis of combined results from 2 double-blind, randomized, placebo-controlled studies. [note: combined analysis with BOLDER I]	Journal of Clinical Psychiatry 69:769-782, 2008.
Olanzapine		
Tohen et al 2003	Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression.	Archives of General Psychiatry 60:1079-1088, 2003.
Shi et al	Effects of olanzapine alone and olanzapine/fluoxetine combination on health-related quality of life in patients with bipolar depression: secondary analyses of a double-blind, placebo-controlled, randomized clinical trial.	Clinical Therapeutics 26:125-134, 2004.
Keck et al	Analyses of treatment-emergent mania with olanzapine/fluoxetine combination in the treatment of bipolar depression.	Journal of Clinical Psychiatry 66:611-616, 2005.
Keck et al	A 24-week open-label extension study of olanzapine-fluoxetine combination and olanzapine monotherapy in the treatment of bipolar depression.	Journal of Clinical Psychiatry 67:798-806, 2006.
Williamson et al	Clinical relevance of depressive symptom improvement in bipolar I depressed patients.	Journal of Affective Disorders 92:261-266, 2006.
Dube et al	Onset of antidepressant effect of olanzapine and olanzapine/fluoxetine combination in bipolar depression.	Bipolar Disorders 9: 618-627, 2007.
Tohen M et al	Effect of comorbid anxiety on treatment response in bipolar depression.	Journal of Affective Disorders 104:137-146, 2007.
Amsterdam & Shults	Comparison of fluoxetine, olanzapine, and combined fluoxetine plus olanzapine initial therapy of bipolar type I and type II major depression - Lack of manic induction.	Journal of Affective Disorders 87:121-130, 2005.

8. Results of Trials

The primary outcome of the quetiapine and olanzapine trials was change in total Montgomery-Asberg Depression Rating Scale (MADRS) scores between baseline and Week 8 of the trials.

The results of the submission's indirect comparison of change in MADRS total score between baseline and Week 8 of quetiapine 300 mg daily versus olanzapine treatment in bipolar I patients using mixed effects model repeat measures (MMRM) analyses indicated that there was no significant difference between quetiapine and olanzapine for the change in total MADRS score between baseline and Week 8.

The pooled efficacy comparisons of change in total MADRS score from baseline to Week 8 are summarised in the table below. Additional analyses, conducted during the evaluation, of the efficacy of quetiapine 300 mg versus quetiapine 600 mg and in bipolar I versus bipolar II patients are also presented in the table below in italics.

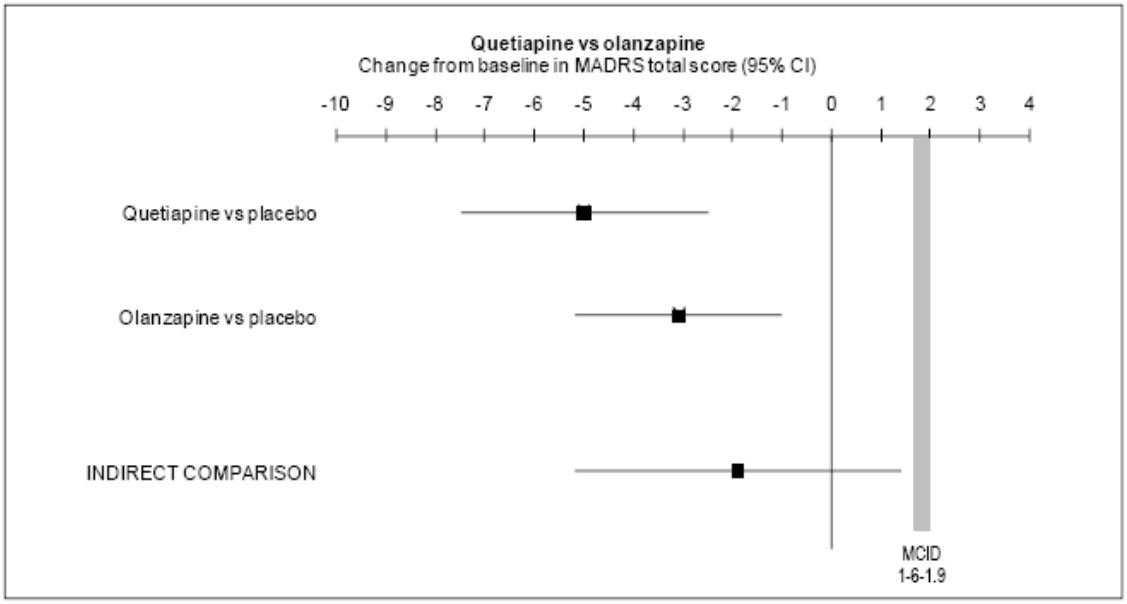
Comparisons	**LOCF** **WMD (95% CI)**	**MMRM** **WMD (95% CI)**
QET 300mg vs placebo (BOLDER I, BOLDER II, EMBOLDEN I AND EMBOLDEN II)		
All patients	**-4.7 (-6.1, -3.2)** N: 811 vs 580	**-4.2 (-6.2, -2.3)** N: 573 vs 370
Bipolar I	**-5.1 (-7.2, -2.9)** N:528 vs 376	**-5.0 (-7.52, -2.48)** N: 362 vs 226
Bipolar II	**-4.1 (-5.9, -2.2)**	**-3.7 (-5.6, -1.8)**

	N: 283 vs 204	N: 211 vs 144
QET 600mg vs Placebo (BOLDER I, BOLDER II, EMBOLDEN I AND EMBOLDEN II)		
All patients	**-4.6 (-5.8, -3.3)** N: 816 vs 580	**-4.5 (-6.5, -2.6)** N: 544 vs 370
Bipolar I	**-5.4 (-7.9, -2.8)** N: 527 vs 376	**-5.3 (-8.2, -2.4)** N:352 vs 226
Bipolar II	**-3.1 (-5.0, -1.3)** N: 289 vs 205	**-3.6 (-5.5, -1.7)** N: 192 vs 144
Olanzapine vs placebo (Tohen 2003)		
Bipolar I	-	**-3.1 (-5.2, -1.0)** N: 179 vs 145
QET 600mg vs QET 300mg		
All patients	-	*-0.34 (-1.53, 0.85)* *N:544 vs 573*
Bipolar I	-	*-0.46 (-1.87, 0.94)* *N: 352 vs 362*
Bipolar II	-	*-0.20 (-1.91, 1.51)* *N:192 vs 211*
Bipolar I versus bipolar II		
Quetiapine 300mg QD	-	*-1.10 (-2.68, 0.47)* *N: 362 vs 211*
Quetiapine 600mg QD	-	*-1.36 (-3.18, 0.46)* *N: 352 vs 192*

Italics indicate additional analyses conducted during the evaluation, bold typography indicates statistically significant results.
Abbreviations: LOCF=last observation carried forward; OC=observed cases analysis (whereby change from baseline was calculated at each assessment); MMRM=mixed effects model repeat measures; MADRS=Montgomery-Asberg Depression Rating Scale; QET=quetiapine; WMD=weighted mean difference.

Both quetiapine 300 mg and 600 mg daily significantly reduced total MADRS scores from baseline to Week 8 compared with placebo treatment. The effects are numerically greater in patients diagnosed with bipolar I disorder compared to bipolar II disorder; however, the differences are not statistically significant. Analyses using mixed effects model repeat measures (MMRM) and last observation carried forward (LOCF) appear to reach similar conclusions.

The mean change from baseline in total MADRS score (MMRM analysis) for the indirect comparison of quetiapine versus olanzapine is shown in the figure below:



The result of the weight adjusted mean difference in change of MADRS total scores from baseline to week 8 for the indirect comparison of quetiapine 300 mg/day versus olanzapine (average daily dose 9.7 mg) via placebo as the common comparator is -1.9 (95% CI: -5.2, 1.4). This is within the non-inferiority threshold nominated by the submission (minimal clinically important difference (MCID) threshold for MADRS between 1.6-1.9).

The following adverse events were reported significantly more for both quetiapine and olanzapine than for placebo: somnolence, weight gain, increased appetite, headache, dry mouth, insomnia, dyspepsia and nausea.

9. Clinical Claim

The submission claimed quetiapine is non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over olanzapine.

The PBAC accepted this claim, however, because olanzapine was not the appropriate comparator for the cost-minimisation analysis presented, this could not be an acceptable basis for the listing.

10. Economic Analysis

The submission presented a cost minimisation analysis. The submission estimated that quetiapine 270.4 mg and olanzapine 9.7 mg daily are equi-effective. However, the additional comparisons conducted during the evaluation demonstrated that there were no significant differences between the outcomes of change in MADRS total score from baseline to Week 8 for patients treated with quetiapine 300 mg daily and quetiapine 600 mg daily. (See Results of Trials: Table with pooled efficacy comparison of change in total MADRS score from baseline to week 8).

Therefore, it might be possible that olanzapine 9.7 mg might also be equivalent to quetiapine 503.9 mg (mean median dose from the quetiapine 600 mg arm of the trials), hence, the dose

relativity of olanzapine : quetiapine in bipolar depression may be between the ratios of 1:27.9 to 1:51.9, i.e., the equi-effective dose may be underestimated.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial savings per year to the PBS to be <$10 million per year in Year 5. The submission's estimate was considered to be an overestimate of the savings.

12. Recommendation and Reasons

The main issue of concern to the PBAC was the choice of comparator. Olanzapine is not TGA registered or PBS listed for acute treatment of depressive episodes in bipolar disorder. The current PBS listing for olanzapine for maintenance treatment of bipolar 1 disorder does not encompass acute treatment of bipolar depression. The PBAC noted therapeutic guidelines indicated that in *de novo* depression the options for treatment include a mood stabiliser (lithium, sodium valproate, carbamazepine, lamotrigine, olanzapine, risperidone and quetiapine) alone or in combination with an antidepressant. Of these, only lithium, carbamazepine and valproate are PBS available for these patients, being unrestricted benefits, and quetiapine appeared to be the only agent with a specific TGA listing for the indication (acute depression). Further, while it was accepted olanzapine is being prescribed for depressive episodes, the results of the expert survey indicated that olanzapine is not the treatment that prescribers would most replace with quetiapine.

The indirect comparison presented indicated there was no significant difference between quetiapine and olanzapine for the change in total Montgomery-Asberg Depression Scale (MADRS) score between baseline and week 8. The PBAC noted the placebo response rate was similar for the two drugs, and hence the direct comparison appeared to be valid. Further, most adverse events reported in quetiapine and olanzapine trials were side effects that have already been identified in patients treated for other disorders.

Therefore, the PBAC accepted the clinical claim that quetiapine could be described as non-inferior in terms of comparative effectiveness and in terms of comparative safety over olanzapine in the treatment of depressive episodes associated with bipolar disorder. However, because olanzapine was not the appropriate comparator for the cost-minimisation analysis presented, this could not be an acceptable basis for listing.

The PBAC did comment that the exclusive consideration of quetiapine 300 mg daily outcomes in the cost-minimisation analysis underestimates the equi-effective dose of quetiapine versus olanzapine, which could be quetiapine 503.9 mg:9.7 mg olanzapine as opposed to 270.4 mg:9.7 mg or very likely, a figure somewhere in between.

With respect to an appropriate cost-effectiveness analysis to justify a listing, the PBAC noted the pre-PBAC response stated data were available for lithium and paroxetine from the two EMBOLDEN studies.

The PBAC rejected listing on the basis the main comparator was inappropriate.

The PBAC noted there is clearly a mismatch between clinical guidelines/common use, TGA registration and current PBS listings and there is a need to get clinical consensus in order for

companies to present appropriate data for TGA/PBS. It was considered this issue needs to be addressed and may require a stakeholder meeting to progress the matter.

The PBAC noted that the submission meets the criteria for an Independent Review.

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

AstraZeneca understands the PBAC's position. There is a clinical need for quetiapine in this population and AstraZeneca is committed to working with the PBAC to reach a satisfactory outcome.