PUBLIC SUMMARY DOCUMENT

Product: Quetiapine fumarate, tablet, 25 mg, 100 mg, 200 mg and 300 mg (base), Seroquel®

Sponsor: AstraZeneca Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

To extend the current authority required PBS listing for quetiapine to include the treatment, as monotherapy, of a patient with bipolar 1 disorder.

2. Background

Quetiapine has not previously been considered by the PBAC for treatment of bipolar 1 disorder.

3. Registration Status

Quetiapine was registered by the TGA on 31 March 2004 as monotherapy for the short-term treatment of acute mania associated with Bipolar 1 Disorder.

Quetiapine is also registered for the treatment of schizophrenia.

4. Listing Requested and PBAC's View

Authority required

As monotherapy for the treatment of bipolar 1 disorder

For PBAC's view, see Recommendation and Reasons

5. Clinical Place for the Proposed Therapy

Bipolar disorder (BPD) (sometimes referred to as manic depression) is a medical condition that affects the brain, causing extreme changes in mood. There are two types of BPD, type 1 defined as having at least one manic episode, with or without depressive episodes, and type two as defined by hypomania and depression.

The atypical antipsychotics are often used to treat patients with BPD. However, individual response, both for efficacy and tolerability, is unpredictable.

Quetiapine is an atypical antipsychotic that will provide an alternative when used as monotherapy to currently available drugs to treat BPD.

6. Comparator

The submission nominated olanzapine as the main comparator. The PBAC considered that the choice of comparator is appropriate for establishing the clinical relativity of quetiapine in bipolar I disorder.

However, for the purpose of establishing pricing relativities the PBAC considered risperidone rather than olanzapine as the relevant comparator because risperidone is listed for the treatment of acute episodes of bipolar 1 disorder, whereas olanzapine is listed for the maintenance treatment of bipolar 1, a broader listing.

7. Clinical Trials

The submission presented as pivotal evidence a comparison of quetiapine and olanzapine in bipolar 1 disorder based on data from two direct randomised, open label trials in adult inpatients with bipolar acute mania or with bipolar affective disorder and schizoaffective disorder, manic or mixed, and an indirect comparison containing four randomised placebo controlled trials in adult inpatients or outpatients with a manic or mixed episode.

The direct comparison trials had been published at the time of submission as follows:

Trial/First author	Protocol title	Publication citation
Belenkaya et al, 2005	Open comparative randomized study efficacy and tolerability of risperidone, olanzapine and quetiapine in acute mania.	European Neuropsychopharmacology 2005; 15 (Suppl 2): S130
Ionescu et al, 2004	Efficacy and tolerability of quetiapine compared with olanzapine for inpatients with acute mania.	European Psychiatry 2004; 19 (Suppl 1): 206S, Abs P26

The indirect comparison trials had been published at the time of submission as follows:

Trial ID	Protocol title/ Publication title	Publication citation
Quetiapine vs placebo		
AZ 104 McIntyre et al, 2005.	Quetiapine or haloperidol as monotherapy for bipolar mania--a 12-week, double blind, randomised, parallel-group, placebo-controlled trial.	European Neuropsychopharmacology; 15(5): 573
AZ 105 Bowden C et al, 2005.	A randomized, double blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder	The Journal of Clinical Psychiatry; 66(1): 111-121
Olanzapine vs placebo		
Tohen et al, 1999	Olanzapine versus placebo in the treatment of acute mania	Am J Psychiatry; 156(6)702-9
Tohen et al, 2000	Efficacy of olanzapine in acute bipolar mania	Arch Gen Psychiatry 2000; 57:841-849

8. Results of Trials

Comparative effectiveness

Direct Comparison

Percentage of responders at Week 6 (response defined as achieving ≥ 50% reduction in Young Mania Rating Scale (YMRS) score)

Trial	Percentage of responders
Belenkaya et al, 2005 - Risperidone (n=15) - Quetiapine (n=15) - Olanzapine (n=15)	 57% 67.8% 63.2%

The percentage of responders trended towards higher levels in the quetiapine group compared to the olanzapine group (67.8% vs 63.2%, respectively) however the statistical significance of the difference was not reported.

Change from baseline in YMRS scores

	Quetiapine			Olanzapine			Risperidone		
	Baseline	Day 42	Change	Baseline	Day 42	Change	Baseline	Day 42	Change
Belenkaya et al, 2005	28±1.6	14.1 ±1.2	49.60 %	26.8±1.5	10.7±1.2	61.00%	26.4±2.1	13.1 ±1.1	50.4%

The percentage change in YMRS scores from baseline to endpoint favours the olanzapine group over the quetiapine group (61% vs 50%, respectively) although the statistical significance of the difference was not reported.

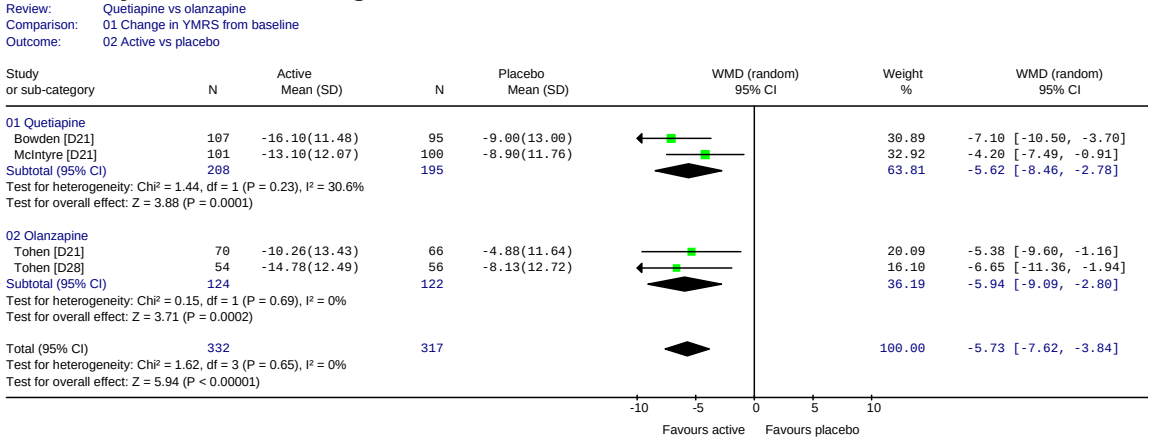
Ionescu et al, 2004 did not report any numerical results but stated that no significant difference between quetiapine (n=16) and olanzapine (n=32) groups was found for any efficacy variable (YMRS score and response rate, and PANSS, CGI-S, CGI-I, GAF scores).

Indirect comparison

The primary outcome in the quetiapine versus placebo studies included in the indirect studies was the mean change from baseline to day 21 in YMRS score. Response rate (defined as a ≥50% decrease in YMRS score from baseline) was a secondary outcome. In the olanzapine versus placebo studies, both the mean change in YMRS score from baseline and response rate (≥50% decrease in YMRS score from baseline) were primary outcomes.

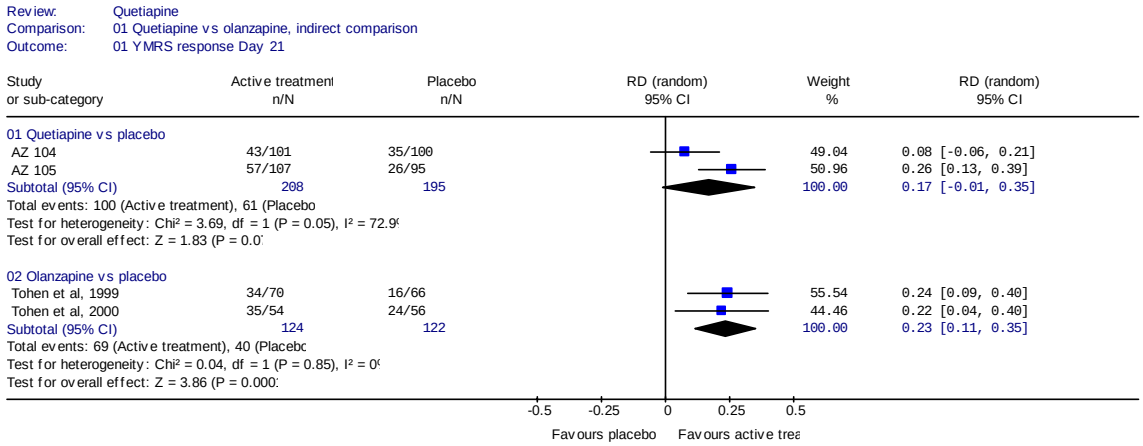
The results of the indirect comparison with placebo as the common reference are reported below.

Meta-analysis of mean change in YMRS total score from baseline, random effects model



Based on the provided results of the meta-analysis of mean change in YMRS total score from baseline, random effects model, the combined estimate appeared to be similar across the two sets of trials and suggested that patients on active treatment (quetiapine or olanzapine) achieved a statistically significant greater mean improvement in YMRS total score than patients on placebo.

Meta-analysis of YMRS response (decrease of ≥50% from baseline in YMRS total score) at Day 21, random effects model



The results appear to suggest that although both sets of trials showed that active treatment resulted in better clinical response compared to placebo at Day 21, the clinical response in the olanzapine-treated patients was statistically significant with a narrower confidence interval and no evidence of heterogeneity.

Comparative toxicity

Direct comparison

Safety results from Belenkaya et al, 2005

Trial ID	Weight gain	EPS	Somnolence and dry mouth
Belenkaya et al, 2005 - Risperidone - Quetiapine - Olanzapine	 13% 6.6% 26%	 33% NR NR	 NR 13% NR
Ionescu et al, 2004			

EPS = Extrapyramidal side-effects

Ionescu et al, 2004 does not present any comparative toxicity results apart from stating "a significant higher percentage of olanzapine treated patients required adjuvant medication for Extra pyramidal symptoms (EPS) or had EPS".

Indirect comparison

Change in Simpson–Angus Scale (SARS) scores from baseline

		Quetiapine			Placebo		
		n	Mean	SD	n	Mean	SD
AZ 104	Day 21	102	-0.8	2.66	101	-0.7	2.45
AZ 105	Day 21	107	-0.8	2.28	95	-0.5	2.65
AZ 104	Day 84	102	-0.8	2.66	101	-0.9	2.47
AZ 105	Day 84	107	-0.8	2.28	95	-0.5	2.65
		Olanzapine			Placebo		
Tohen et al, 1999	Day 21	68	-0.15	2.12	63	0.05	1.88
Tohen et al, 2000	Day 28	54	-0.27	1.16	56	0.13	1.61

Change in Barnes Akathisia Scale (BARS) scores from baseline

		Quetiapine			Placebo		
		n	Mean	SD	n	Mean	SD
AZ 104	Day 21	102	-0.2	0.74	101	-0.1	0.73
AZ 105	Day 21	107	0	0.39	95	0	0.58
AZ 104	Day 84	102	-0.2	0.71	101	-0.2	0.64
AZ 105	Day 84	107	0	0.37	95	0	0.55
		Olanzapine			**Placebo**		
Tohen et al, 1999	Day 21	70	-0.17	0.8	66	-0.11	0.64
Tohen et al, 2000	Day 28	54	-0.40	0.83	56	-0.16	0.76

In regard to the olanzapine trials, olanzapine-treated patients showed an improvement in parkinsonism (SARS) and akathisia (BARS) from baseline to end point, whereas placebo-treated patients experienced a worsening in Parkinsonism and an improvement in akathisia. However, these differences are not statistically significant. In comparison, both the active treatment and placebo arms in the quetiapine trials demonstrated improvement in Parkinsonism and akathisia.

Mean weight gain/loss from baseline across the randomised trials

Trial ID	Quetiapine	Placebo	Olanzapine	Difference vs placebo
Day 21				
AZ 104	0.3kg ± 2.23	-0.1kg ± 1.11		0.4kg, p NR
AZ 105	1.1kg ± 2.06	-0.4kg ± 1.95		1.5kg, p NR
Tohen et al, 1999		-0.44 kg ± 2.35	1.65 kg ± 2.54	2.09kg, p<0.001
Day 28				
Tohen et al, 2000		0.45kg ± 2.30	2.1kg ± 2.80	1.65kg, p=0.002
Day 84				
AZ 104	0.9kg ± 3.55	-0.3kg ± 2.55		1.2kg, p NR
AZ 105	2.6kg ± 4.23	-0.1 ± 3.34		2.7kg, p NR
Pooled result (random effects)				
Chi-square for heterogeneity: *P*= I^2 statistic with 95% uncertainty interval =				

The results at Day 21/28 indicate that olanzapine-treated patients had a greater mean weight gain than quetiapine-treated patients.

9. Clinical Claim

The submission claimed that quetiapine is no worse than olanzapine in terms of effectiveness and toxicity.

For PBACs view of this claim *See Recommendations and Reasons*

10. Economic Analysis

The submission presented a cost-minimisation analysis. The PBAC noted the trial data indicated that the equi-effective doses for the treatment of bipolar disorder are quetiapine 29 mg (base) for 42 days and olanzapine 1 mg for 42 days, and that the equi-effective doses for the treatment of bipolar disorder for risperidone and olanzapine are 3.75 mg per day and 10.4 mg per day. These values indicated the equi-effective doses for the treatment of bipolar disorder are approximately quetiapine 300 mg (base) per day and risperidone 3.75 mg per day.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of packs dispensed/year to be in the range 100,000 – 200,000 in Year 5.

The submission estimated the listing would be associated with the financial savings/year to the PBS (excluding co-payments) minus any savings in use of other drugs to be less than $1 million in Year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended the listing of quetiapine for the treatment, as monotherapy, of an acute episode of mania associated with bipolar 1 disorder on a cost-minimisation basis compared with olanzapine. The PBAC considered quetiapine to be no worse than olanzapine in terms of safety and efficacy. However, the Committee had some remaining doubts about the evidence provided to support the claim, given that the direct randomised trials were small and used an open label design, while the trials in the indirect comparison differed significantly in aspects of trial design and patient characteristics.

Recommendation

QUETIAPINE FUMARATE, tablet, 25 mg, 100 mg, 200 mg and 300 mg (base)

Restriction:	Authority required Monotherapy, for up to 6 months, of an episode of acute mania associated with bipolar 1 disorder.
Maximum Quantity:	60 (25mg, 200mg, 300 mg), 90 (100 mg)
Number of repeats:	5 (all strengths)

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 Australia welcomes the PBAC recommendation for Seroquel to be listed on the PBS, to provide access to an additional treatment option for patients diagnosed with acute mania associated with bipolar I disorder.