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

The submission sought an extension to the current Authority Required (Streamlined) listing for immediate release quetiapine to include maintenance treatment of bipolar disorder, in combination with a mood stabiliser, for the prevention of recurrence of manic, depressive or mixed episodes.

2. Background

The requested indication for the drug 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 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

<u>Authority Required (STREAMLINED)</u>
Maintenance treatment of bipolar I disorder, in combination with a mood stabiliser, for the prevention of recurrence of manic, depressive or mixed episodes.

For PBAC views see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Bipolar I disorder is a psychiatric condition that is characterised by the occurrence of one or more manic episodes or mixed episodes. Often individuals have also had one or more major depressive episodes.

Treatment to prevent recurrence of mania or depression is termed maintenance treatment.

Quetiapine in combination with a mood stabiliser offers an alternative therapy for the maintenance treatment of bipolar 1 disorder.

6. Comparator

The submission nominated olanzapine as the comparator.

The PBAC accepted that olanzapine was the appropriate comparator.

7. Clinical Trials

The submission presented two randomised trials comparing quetiapine (flexible doses quetiapine 400-800 mg/day) versus placebo and one randomised trial of olanzapine versus placebo (Tohen *et al* 2004) in maintenance treatment of bipolar I disorder (olanzapine 5-20 mg/day flexible dosing) in combination with either lithium or valproate. The basis of the submission was an indirect comparison of the quetiapine and olanzapine trial outcomes using placebo as a common comparator.

One of these studies had been published at the time of the submission, as follows:

Trial/First author	Protocol title	Publication Citation
Common reference: Placebo		
Olanzapine		
Tohen *et al* (2004)	Double-blind RCT; Compares the time to mood event of OLZ + LI/VAL vs PLA + LI/VAL for participants in syndromic remission of Bipolar I disorder for up to 18 months.	
	Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone.	British Journal of Psychiatry, 184, 337-345, 2004.

Abbreviations: RCT=randomised controlled trial; OLZ=olanzapine; LI=lithium; VAL=valproate; PLA=placebo.

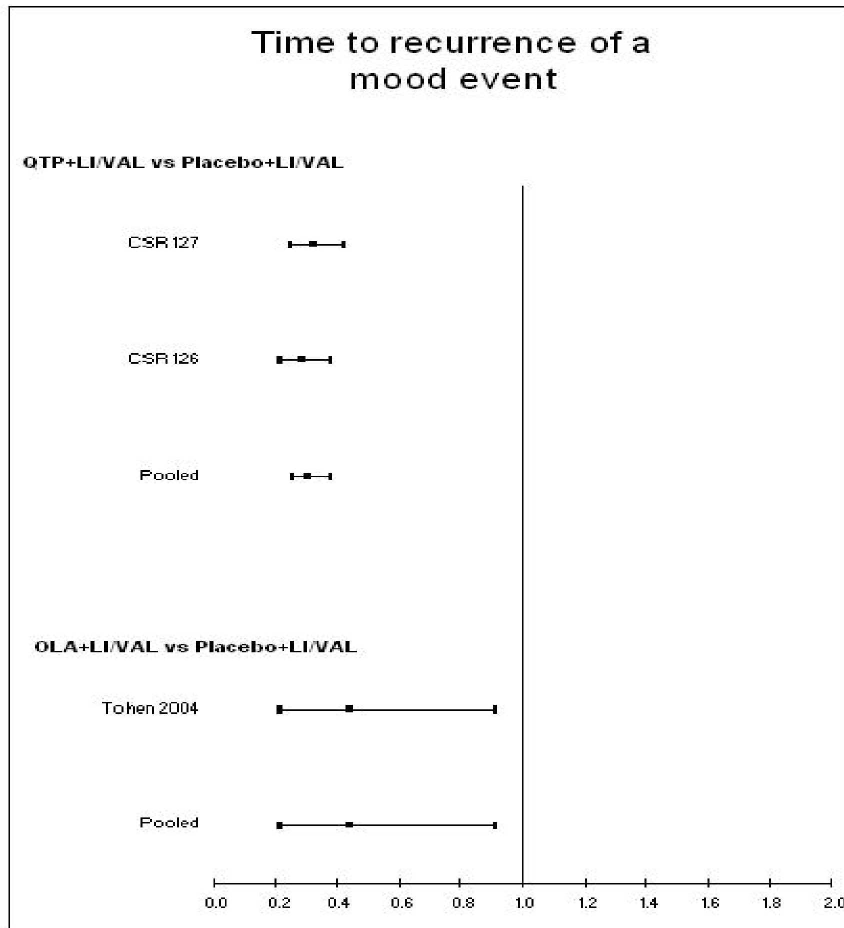
8. Results of Trials

The results of the indirect comparison between quetiapine and olanzapine via placebo as common comparator for the outcome of time to recurrence of mood event are presented in the table below.

Trial ID	QTP + MS vs PLA + MS HR (95% CI)	OLZ + MS vs PLA + MS HR (95%CI)	QTP + MS vs OLZ + MS Indirect HR (95% CI)	Log rank *p* value
Study 1[a]	***0.28 (0.21, 0.37)***	-	-	<0.0001
Study 2[a]	***0.32 (0.24, 0.42)***	-	-	<0.0001
Tohen *et al* (2004)	-	**0.44 (0.21, 0.91)**	-	0.023
Pooled[b]	**0.30 (0.25,0.37)**	**0.44 (0.21, 0.91)**	0.69 (0.32,1.47)	-

Abbreviations: OLZ=olanzapine; MS=mood stabiliser (either valproate or lithium); PLA=placebo; QTP=quetiapine; CI=confidence interval;
[a] primary outcome in the trial
[b] pooled using the random effects model

The figure of the forest plot of time to recurrence of mood event across the indirectly compared randomised trials (hazard ratio) is shown below:



The detail above illustrates results of time to recurrence of any mood event. The time to recurrence of an event is reported as a hazard ratio (HR) in all three trials. Time to recurrence of a mood event was significantly longer in patients treated with quetiapine in combination with valproate or lithium compared to valproate or lithium alone (pooled HR: 0.30, 95%CI: 0.25, 0.37) representing a 70% reduction in risk. Time to symptomatic relapse of a mood event was also statistically longer in patients treated with olanzapine plus valproate or lithium compared to valproate or lithium alone (HR: 0.44, 95% CI: 0.21, 0.91) representing a 56% risk reduction.

Most adverse events reported in quetiapine and olanzapine trials were side effects that had already been identified in patients treated with these agents for other disorders. The submission indirectly compared the incidence diarrhoea, insomnia, somnolence, tremor and weight gain between quetiapine and olanzapine treated patients in the randomised trials. From the submission's analyses, patients treated with quetiapine were more likely to experience somnolence compared to olanzapine treated patients (quetiapine (QTP) versus olanzapine (OLZ): RR: 11.03 (1.10, 110.37)), the incidence of diarrhoea, insomnia, tremor and weight gain did not appear to be significantly different.

9. Clinical Claim

The submission claimed quetiapine as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over olanzapine when used in combination with either lithium or valproate.

While the PBAC considered there was uncertainty in the interpretation of the data based on an indirect comparison with placebo as the common reference, it agreed that overall, the assumption that quetiapine was no worse than olanzapine reasonable.

10. Economic Analysis

The submission presented a cost-minimisation analysis. The equi-effective doses estimated as quetiapine 506.8 mg and olanzapine 8.6 mg/day were considered reasonable.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely treatment cost of equi-effective dose of quetiapine and olanzapine to be less than $10 million per year. The submission estimated potential savings to the PBS would be approximately $11,000 in Year 5.

For PBAC's view see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended the listing of quetiapine fumarate for the maintenance treatment of bipolar I disorder, in combination with lithium or sodium valproate on the basis of cost-minimisation with olanzapine and where the equi-effective doses are quetiapine 506.8 mg per day and olanzapine 8.6 mg per day, i.e., a dose relativity of 58.9:1.

The PBAC accepted that olanzapine was the appropriate comparator. The PBAC considered the restriction should reflect the Therapeutic Goods Administration (TGA) approved indication that use of quetiapine be in combination with either lithium or sodium valproate.

While the PBAC considered there was uncertainty in the interpretation of the data based on an indirect comparison with placebo as the common reference, it agreed that overall the assumption that quetiapine was no worse than olanzapine was not unreasonable. The PBAC did note that the ways in which mood events were defined differed between the quetiapine and olanzapine trials. Also, the size of the olanzapine trial was smaller than for quetiapine and thus while there is no significant difference between olanzapine and placebo this could be due to inadequate power due to small sample size.

The PBAC noted the potential savings may be an overestimate as the submission's estimate did not consider any potential switching of patients from other existing PBS-listed therapies used in combination. The Committee commented that, as quetiapine is listed as a streamlined authority, it may be difficult to calculate the weighted average price as the proportion of usage in the current indications and the new indication will be unknown.

Recommendation:
QUETIAPINE FUMARATE, tablets, 25 mg, 100 mg, 200 mg, 300 mg (base).

Extend the listing as follows to include:

Restriction:	Authority Required (STREAMLINED) Maintenance treatment of bipolar I disorder, in combination with lithium or sodium valproate.

Max. Qty: 60 (25 mg, 200 mg and 300 mg), 90 (100 mg)
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

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