PUBLIC SUMMARY DOCUMENT
Product: Quetiapine, tablets, 25 mg, 100 mg, 200 mg and 300 mg (as fumarate), Seroquel®, and tablets (modified release), 50 mg, 200 mg, 300 mg and 400 mg (as fumarate), Seroquel XR®
Sponsor: AstraZeneca Australia Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission sought an Authority Required (Streamlined) listing for 'adjunctive therapy to mood stabilisers, for up to 6 months, of an episode of acute mania associated with bipolar I disorder'.

2. Background

For background information on previous PBAC considerations of quetiapine, refer to the July 2010 Public Summary Document (PSD) for quetiapine available at: www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Quetiapine-july10.

3. Registration Status

On 17 October 2008 quetiapine was registered by the TGA for the treatment of acute mania associated with bipolar I disorder in combination with lithium or sodium valproate.

Other registered bipolar disorder indications for the immediate and modified release formulations include:

- Maintenance treatment of bipolar 1 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 acute mania associated with bipolar I disorder as monotherapy.
- Treatment of depressive episodes associated with bipolar disorder

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Adjunctive therapy to mood stabilisers for up to 6 months, of an episode of acute mania associated with bipolar I disorder.

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

Bipolar disorder is a psychiatric illness that is characterised by one or more manic, depressed or mixed episodes. The listing requested would provide an additional atypical antipsychotic treatment option for adjunctive therapy of mania associated with bipolar disorder.

6. Comparator

The submission nominated risperidone as the comparator as it was the only atypical antipsychotic drug subsidised on the PBS for use as adjunct therapy for acute mania in bipolar I disorder. This was previously considered appropriate by the PBAC.

7. Clinical Trials

The basis of the submission was two direct randomised placebo-controlled trials (RCTs) of quetiapine as adjunct therapy to a mood stabiliser (lithium or sodium valproate) (CSR99 and

CSR100), and two of risperidone as adjunct therapy to a mood stabiliser (lithium, sodium valproate or carbamazepine) (Yatham 2003 & Sachs 2002). The submission undertook an indirect comparison of quetiapine and risperidone as adjunct treatment to mood stabilisers, using placebo as the common comparator.

The studies published at the time of the submission are as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Quetiapine + mood stabiliser vs placebo+ mood stabiliser		
CSR 99/ Sachs G et al	Quetiapine with lithium or valproate for the treatment of bipolar mania: a randomised, double-blind, placebo-controlled study.	Bipolar Disorders 2004; 6: 213-223
CSR 100/ Yatham L et al	A double blind, randomized, placebo-controlled trial of quetiapine as an add-on therapy to lithium or valproate for the treatment of bipolar mania.	International Clinical Psychopharmacology 2007: 212-220
Risperidone + mood stabiliser vs mood stabiliser + placebo		
Yatham L et al	Mood stabilisers plus risperidone or placebo in the treatment of acute mania: International, double-blind, randomised controlled trial.	British J Psych 2003 (182) 141-147
Sachs G et al	Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double blind placebo-controlled comparison of efficacy and safety.	Am J Psychiatry 2002 (159): 1146-1154

8. Results of Trials

The following tables summarise the results of the indirect comparison of quetiapine and risperidone for the primary and secondary outcomes of the trials.

Summary of results of the indirect comparison for the primary outcome – change in YMRS from baseline to day 21 (mITT, LOCF)

	Trials of quetiapine			Trials of risperidone		
Trial ID	**Tmt effect WMD (95%CI)**	**QET + mood stabiliser Mean**	**PBO + mood stabiliser Mean**	**PBO + mood stabiliser Mean**	**RISP + mood stabiliser Mean**	**Tmt effect WMD (95% CI)**
Quetiapine BID vs risperidone QD (including CBZ)						
CSR 99	*-3.83 (-8.19, 0.53)*	-13.76	-9.93	-	-	-
CSR 100	*-2.0 (-6.81,2.81)*	-15.2	-13.2	-	-	-
Yatham 2003				-10.3	-14.5	***-4.20 (-8.22, -0.18)***
Sachs 2002	-	-	-	-8.2	-14.3	***-6.10 (-10.08, -2.12)***
Pooled[a]	*-3.01 (-6.23, 0.22)*	-	-		-	***-5.16 (-7.99, -2.32)***
Indirect estimate of effect[b] (95% CI)				*2.15 (-2.14, 6.44)*		
Quetiapine BID vs risperidone QD (excluding CBZ)						
CSR 99	*-3.83 (-8.19, 0.53)*	-13.76	-9.93			
CSR 100	*-2.0 (-6.81, 2.81)*	-15.2	-13.2			

Trial ID	Trials of quetiapine			Trials of risperidone		
	Tmt effect WMD (95%CI)	**QET + mood stabiliser Mean**	**PBO + mood stabiliser Mean**	**PBO + mood stabiliser Mean**	**RISP + mood stabiliser Mean**	**Tmt effect WMD (95% CI)**
Yatham 2003				-9.80	-15.20	**-5.40 (-9.84,-0.96)**
Sachs 2002	-	-	-	-8.20	-14.30	**-6.10 (-10.09,-2.11)**
Pooled[a]	*-3.01 (-6.23, 0.22)*					**-5.79 (-8.76, -2.82)**
Indirect estimate of effect[b] (95% CI)				2.78 (-1.60, 7.16*)*		

Bold =statistical significance. *Italics= updated during the evaluation.*

Abbreviations: mITT= modified intention to treat population (treated and analysed patients); LOCF= last observation carried forward; WMD= weighted mean difference; QET= quetiapine; PBO= placebo; RISP= risperidone; CSR= Clinical Study Report; CI = confidence interval; *n* = number with event; *N* = number in group; RR = relative risk

[a] pooled using the random effects model

[b] inferred as proposed drug over main comparator

Summary of results of the indirect comparison for 'YMRS response' (≥50% change in YMRS)

Trial ID	Trials of quetiapine			Trials of risperidone		
	Tmt effect RR (95% CI)	**QET + mood stabiliser Resp. (%)**	**PBO + mood stabiliser Resp. (%)**	**PBO + mood stabiliser Resp. (%)**	**RISP + mood stabiliser Resp. (%)**	**Tmt effect RR (95% CI)**
mITT analysis (treated and analysed population)						
CSR 99	***2.60 (1.70, 4.09)***	45/81 (56%)	19/89 (21%)	--	--	--
CSR 100	*1.13 (0.88, 1.48)*	59/104 (57%)	48/96 (50%)	--	--	--
Yatham 2003	--	--	--	30/73 (41%)	40/69 (59%)	***1.41 (1.01, 2.00)***
Sachs 2002	--	--	--	NR	NR	--
Pooled[a]	*1.69 (0.73, 3.88)*	104/185 (56%)	67/185 (36%)	30/73 (41%)	40/69 (59%)	***1.41 (1.01, 2.00)***
Indirect estimate of effect[b](95% CI)				*1.19 (0.49, 2.96)*		
ITT analysis (randomised population)						
CSR 99	***2.60 (1.67, 4.13)***	*45/91 (49%)*	*19/100 (19%)*	--	--	--
CSR 100	*1.22 (0.93, 1.60)*	*59/106 (56%)*	*48/105 (46%)*	--	--	--
Yatham 2003	--	--	--	*30/76 (39%)*	*40/75 (53%)*	*1.35 (0.95, 1.92)*
Sachs 2002	--	--	--	NR	NR	--
Pooled[a]	*1.74 (0.81, 3.73)*	*104/197 (53%)*	*67/205 (33%)*	*30/76 (39%)*	*40/75 (53%)*	*1.35 (0.95, 1.92)*
Indirect estimate of effect [b] (95% CI)				*1.29 (0.56, 2.99)*		

Bold =statistical significance. *Italics= updated during the evaluation.*

Abbreviations: QET=quetiapine; RISP= risperidone; CI = confidence interval; n = number with event; N = number in group; RR = relative risk; Resp= response; REM= random effects model.

[a] pooled using the random effects model

[b] inferred as proposed drug over main comparator

For PBAC's view of these results, see Recommendation and Reasons

The submission reported that the pooled analysis of the two quetiapine trials (Yatham L, et al. *Quetiapine versus placebo in combination with lithium or valproate for the treatment of bipolar mania*. J Clin Psychopharmacology 2004(24); 6: 599-606) showed quetiapine was associated with a significantly higher proportion of patients achieving YMRS response (RR 1.34, 95% CI 1.08, 1.66). Using the random-effects model used in the evaluation, there was no significant improvement in the pooled analysis of the CSR 99 and CSR 100 for the modified intention to treat population (treated and analysed patients) (RR 1.69 95% CI 0.73, 3.88) or the intention to treat (ITT) population (RR 1.74 95% CI 0.81, 3.73).

Risperidone (Yatham 2003) was associated with significantly more patients achieving YMRS response than placebo, however the lower boundary of the confidence interval was close to the boundary for no-effect (RR 1.41 95% CI 1.01, 2.00). The data for the population excluding the patients treated with carbamazepine was not reported for the YMRS response outcome, so it was not possible to determine if risperidone was associated with a significant improvement in the patients treated with other mood stabilisers (lithium and sodium valproate).

One of the main issues was whether it is appropriate to conduct an indirect comparison of quetiapine and risperidone using these data, given the differences between the trial populations. Key issues of difference were that the baseline YMRS scores for risperidone were lower than the quetiapine trials and that most patients in the quetiapine trials were already receiving a mood stabiliser at baseline; whereas, the risperidone trials enrolled patients who initiated risperidone concurrently with a mood stabiliser.

The submission claimed the results of the indirect comparisons indicated there was no significant difference between quetiapine and risperidone in terms of YMRS response. Given the issues identified above, and that the indirect comparison was based on secondary outcomes from the trials, this conclusion should be interpreted with caution.

In the clinical trials, quetiapine was associated with significantly more somnolence, dry mouth, asthenia and postural hypotension than placebo. Risperidone was associated with a higher rate of extrapyramidal-related adverse effects in Yatham 2003. All trials reported a statistically significant weight gain in patients who received active atypical antipsychotic treatment. Overall, the submission did not provide convincing evidence that quetiapine and risperidone had comparable safety and tolerability profiles. However, given the limited data available from the trials further information to inform this comparison was unlikely to be forthcoming.

9. Clinical Claim

The submission described quetiapine as non-inferior to risperidone in terms of comparative effectiveness and equivalent in terms of comparative safety. The PBAC considered that the evidence presented did not support this claim given the identified issues with the trials included in the indirect comparisons.

10. Economic Analysis

The submission presented a cost-minimisation analysis. Quetiapine 474.80 mg was assumed to be equivalent to risperidone 3.92 mg, corresponding to a dose relativity of 121.18 mg: 1 mg for quetiapine and risperidone.

11. Estimated PBS Usage and Financial Implications

No estimate of the likely number of patients per year prescribed quetiapine for this indication was provided in the submission. The submission considered a quetiapine listing for adjunct therapy to mood stabilisers for acute mania with bipolar I disorder would be cost-neutral, because of the cost-minimisation approach used in economic evaluation.

12. Recommendation and Reasons

The submission claimed that quetiapine demonstrated a statistically significant improvement over placebo with respect to the primary outcome, change in total YMRS score from baseline to day 21, in CSR 99 but not CSR 100. When the appropriate random-effects model was used, neither CSR 100 nor CSR 99 showed a statistically significant benefit over placebo for change in YMRS. The random effects meta-analysis of the quetiapine data also demonstrated that the change in YMRS is no longer statistically significant, with a weighted mean difference (WMD) -3.01 (-6.23, 0.22). When the random-effects model was used to meta-analyse the risperidone data, the change in YMRS was statistically significant for both the overall analysis, WMD -5.16 (-7.99, -2.32), and the analysis excluding patients who were treated with carbamazepine, WMD -5.79 (-8.76, -2.82).

The indirect comparisons demonstrated no significant difference between risperidone and quetiapine at the 5% level, but the associated 95% confidence intervals were wide and included the minimum clinically important difference (MCID) (4-6 points on the YMRS scale). Therefore, a clinically important difference between quetiapine and risperidone cannot be ruled out. The placebo response in trial CSR 100 (international, multi-centre trial) was more than double that in CSR 99 (US trial), also suggesting there are considerable differences in the populations included in these trials. Cochran's Q statistic was significant (8.33, p=0.0039), corresponding to an I^2 statistic of 88%, indicating high heterogeneity. This was likely to invalidate the results of the meta-analysis of quetiapine trials and the inclusion of the pooled effect in the indirect comparison.

Overall, the PBAC was of the opinion that differences in mood stabiliser use and YMRS score at baseline demonstrated that there were important differences in the trial populations, which may invalidate the indirect comparison between risperidone and quetiapine.

The PBAC rejected listing on the basis that quetiapine as add-on therapy to lithium or valproate had not demonstrated non-inferiority to the comparator and as such was not acceptable for consideration in a cost minimisation analysis.

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

The sponsor is disappointed at this outcome.