Public Summary Document

Product: Quetiapine, tablets (modified release), 50 mg, 150 mg, 200 mg and 300 mg, Seroquel XR®
Sponsor: AstraZeneca Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The resubmission requested an Authority required (Streamlined) listing for recurrent major depressive disorder (MDD) as augmentation to current antidepressant therapy in patients treated by a psychiatrist or a GP in consultation with a psychiatrist who have had inadequate response to two prior antidepressant therapies.

2. Background

This was the second consideration of quetiapine in major depressive disorder.

In November 2011, the PBAC rejected a submission seeking to extend quetiapine's (modified release) current Authority required (Streamlined) listing to include use as adjunctive therapy in the treatment of Treatment Resistant Depression (TRD), also referred to as Major Depressive Disorder (MDD), on the basis of inadequate clinical evidence to support a claim of superiority over the nominated comparator and therefore the cost-effectiveness analysis was not accepted.

3. Registration Status

Quetiapine modified release tablets were TGA approved on 3 June 2009 for the following indication:
Treatment of recurrent major depressive disorder (MDD) in patients who are intolerant of, or who have an inadequate response to alternative therapies.

4. Listing Requested and PBAC's View

Authority required (Streamlined)
Initial treatment of recurrent major depressive disorder as augmentation to current antidepressant therapy in a patient who has had inadequate response to two prior antidepressant therapies. The patient must be treated by a psychiatrist or a general practitioner in consultation with a psychiatrist.

Authority required (Streamlined)
Continuing treatment of recurrent major depressive disorder as augmentation to current antidepressant therapy in a patient who has had inadequate response to two prior antidepressant therapies. The patient must be treated by a psychiatrist or a general practitioner in consultation with a psychiatrist.

The PBAC recalled that quetiapine had previously been submitted as a Streamlined Authority for "adjunctive therapy in treatment resistant major depression". The PBAC recalled that it considered that this proposed restriction would have allowed use in a broad patient population, as no definition of 'treatment resistant major depression' was included.

The PBAC noted that the restriction proposed in this resubmission specified that treatment must be as augmentation to current antidepressant therapy, following inadequate response to two prior antidepressant therapies. The PBAC considered the proposed restriction to be appropriate.

5. Clinical Place for the Proposed Therapy

Major depressive disorder (MDD) is a disabling illness that leads to a considerable reduction in quality of life at a cost to society. Although antidepressants are used in the treatment of MDD, some patients do not achieve full remission i.e. absence of symptoms and full return to pre-morbid functioning. TRD is characterised by an inadequate response subsequent to two lines of adequate antidepressant therapy in patients with MDD.

The submission proposed that the place in therapy of quetiapine modified release tablets is as an adjuvant (add-on therapy) to ongoing antidepressant therapy in patients with recurrent MDD/TRD, who have failed at least two antidepressant therapies.

6. Comparator

The re-submission nominated lithium as the main comparator. At the November 2011 meeting, the PBAC considered that although lithium was an appropriate comparator, electroconvulsive therapy (ECT) may also be considered. The submission agreed there is a slight possibility of a reduction in ECT if quetiapine XR was PBS listed for the proposed restriction, but did not consider it an appropriate comparator as ECT is generally only considered after all pharmacological agents had failed.

The PBAC considered this reasonable and accepted lithium as the comparator.

7. Clinical Trials

As in the July 2011 submission, the re-submission presented the RUBY trial, a six-week, open-label, rater-blinded randomised trial comparing quetiapine XR augmentation (titrated to 300 mg/day) with lithium (900 mg/day) augmentation.

The relative efficacy of quetiapine XR to lithium was tested using rater-reported change in the Montgomery-Asberg Depression Rating Scale (MADRS) score (0-60, with higher scores indicating greater severity of depression). A total of 668 patients with TRD having failed one or two prior antidepressant therapies were enrolled in the RUBY trial.

The previous analysis argued a 95% confidence interval to support superiority based on the change in MADRS score. This has been replaced in the re-submission with the predetermined study confidence interval of 97.5%.

The RUBY trial study protocol pre-determined that non-inferiority would be satisfied based on a difference of three points or less on the MADRS score. The re-submission also acknowledged a recent study by Duru & Fantino (2008) that identified a minimally clinically important difference (MCID) threshold associated with high test-retest reliability ranging from 1.6 to 1.9 points on the MADRS scale.

The published trials and associated reports presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
RUBY		
Franco Martin et al.	Quetiapine XR monotherapy and quetiapine XR+ongoing antidepressant versus lithium+ongoing AD for Stage II treatment-resistant major depressive disorder.	*European Neuropsychopharmacology* (2010); 20: S347. [abstract only]
Bauer et al.	Predictive factors of remission for treatment-resistant major depressive disorder (MDD) during treatment with extended-release quetiapine fumarate (quetiapine XR).	*International Journal of Psychiatry in Clinical Practice* (2010b); 14: 20-21. [abstract only]
Bauer et al.	Quetiapine xr monotherapy, quetiapine XR+ongoing antidepressants and lithium+ongoing antidepressants in patients with treatment-resistant major depressive disorder.	*International Journal of Neuropsychopharmacology* (2010a); 13: 143. [abstract only]

8. Results of Trials

The previous submission argued that quetiapine XR augmentation was superior to lithium augmentation. The re-submission argued non-inferiority of quetiapine XR to lithium.

The PBAC had expressed concern about the previous submission's analyses based on a modified intention-to-treat (mITT) population, and noted that the re-submission instead conducted a Per Protocol (PP) analysis in patients with adequate lithium levels. The PBAC noted that 112 out of 221 patients in the RUBY trial with lithium levels still outside the range 0.6-1.2 mmol/L at the sixth and final weekly visit were excluded from the PP population.

The PBAC considered that given that approximately half of the patients in the trial did not achieve a lithium level in the target range, it was probable that lithium was under dosed at 900 mg per day. In addition, the PBAC noted that the trial design specified that patients whose lithium level was in the target range at the point of the sixth week therefore had adequate lithium levels. Patients whose lithium level may have been adequate at the final visit may have achieved adequate levels only shortly before the final visit.

The submission argued that the treatment effect observed in RUBY is consistent with that in ONYX and PEARL, both double blinded, placebo-controlled trials, suggesting the impact of the open-label nature of the RUBY trial was minimal.

The resubmission claimed a usual effective dose of 300 mg; however the PBAC noted that the Product Information states a usual effective dose of 150 mg. The recommended dose in the PI ranges up to 300 mg. The PBAC noted the results of ONYX and PEARL showed mixed results in placebo comparator trials, with the PEARL trial finding no statistically significant difference between quetiapine XR 150 mg and placebo.

The results for change at six weeks from baseline in MADRS score in Quetiapine XR trials (mITT analysis) are shown in the following table:

mean (SE)	Quetiapine XR 300 mg	Quetiapine XR 150 mg	Lithium	Placebo	LS mean change difference, 300 mg (95% CI)
RUBY [a]	-17.2 (0.83)		-14.9 (0.97)		-2.32 (-4.31, 0.33)
ONYX [b]	**-15.0 (9.0)** [d]	**-15.4 (NR)**		-12.1 (10.1) [d]	**-2.73 (-4.62, -0.84)**
PEARL [c]	**-14.7 (NR)**	-13.6 (NR)		-11.7 (NR)	NR

MADRS = Montgomery-Asberg depression rating scale; NR = not reported; SE = standard error; LS = least square; CI = confidence interval; N = trial population; **bold** = statistically significantly different compared to placebo.
[a] RUBY: quetiapine XR N=183; Lithium N=109;
[b] ONYX; quetiapine XR 300 mg N=161; quetiapine XR 150 mg N= 166 placebo N=160;
[c] PEARL: quetiapine XR 300 mg N=146; quetiapine XR 150 mg N = 143 placebo N=143.
[d] Standard deviation

The PBAC considered that the open-label design of the RUBY trial introduced some risk of bias, but this was mitigated by use of blinded assessors, and the standard rating scale (MADRS).

However, the PBAC considered that the reliability of the RUBY trial was significantly affected by the lack of adequate follow-up after the six week duration of the trial. The PBAC considered also that the missing data, managed in the submission by last observation carried forward analysis, remained problematic.

The results of change in MADRS total score from randomisation, RUBY trial, last observation carried forward, per protocol population are shown in the following table:

Analysis	Quet XR aug	Lithium aug	Difference MADRS [b] Quet XR aug vs Lithium aug	P value
All previous failures				
N	183	109		
ANCOVA [a] LS Mean	-17.2 (-18.8, -15.6)	-14.9 (-16.8, -12.9)	**-2.3 95% CI: -4.31, -0.33 97.5% CI: -4.60, -0.05**	**0.0223**
One previous failure				
N	91	59		
ANCOVA [a] LS Mean	-18.7 (-20.8, -16.5)	-16.3 (-18.7, -13.8)	-2.5 95% CI: -5.10, 0.18 97.5% CI: -5.48, 0.57	0.0661
Two previous failures				
N	92	50		
ANCOVA [a] LS Mean	-15.8 (-18, -13.7)	-14.3 (-17, -11.6)	-1.59 95% CI: -4.84, 1.65 97.5% CI: -5.3, 2.1	0.3311

ANCOVA – Analysis of Covariance, CI – Confidence Interval, LS – Least Squares, MADRS – Montgomery-Asberg Depression Rating Scale.
[a] Analyses are adjusted for treatment, centre, baseline MADRS, stratified group
[b] The MADRS ranges from 0-60, with higher scores indicating greater severity of depression.

The results showed a small but statistically significant improvement in MADRS scores, favouring quetiapine XR. The re-submission concluded non-inferiority of quetiapine XR to lithium, given that the difference in MADRS score change was less than three points.

The difference in MADRS score was notably smaller in the subgroup of patients who failed two prior treatments, compared to the patient who failed only one prior treatment. It was close to the minimum clinically important difference (MCID), identified in the literature as being 1.6-1.9 on the MADRS scale (0-60).

The clinical study report for the RUBY trial indicated a sample size (N) of 192 would be needed to demonstrate pair-wise equivalence according to the study protocol. Although the results indicated a non-statistically-significant difference between the means (i.e. non-inferiority for participants with two previous failures), the PBAC did not consider this sub-group analysis to be reliable.

Overall, the PBAC did not consider that the clinical data supported the submission's claim of non-inferior comparative effectiveness.

With regard to comparative harms, the re-submission presented the same results as in the previous submission. The occurrence of specific adverse events was different for quetiapine and lithium. Quetiapine XR treatment was mostly associated with dry mouth, somnolence, fatigue, sedation, dizziness and weight gain, while lithium was mostly associated with nausea, tremors and diarrhoea.

The PBAC expressed particular concern that 14 of 231 patients on quetiapine gained more than 7% of their body weight over the course of the six week trial. The PBAC noted the potential flow-on health consequences of weight gain with regard to incidence of diabetes in younger patients most likely to be prescribed quetiapine for this indication.

The PBAC noted that 5 patients (2.2%) in the quetiapine XR group suffered serious adverse events (SAEs), while 1 patient (0.4%) in the add-on lithium group had SAEs. 23 patients (10%) on quetiapine had AEs leading to discontinuation, compared with 18 patients (7.9%) in the add-on lithium group. The proportion of patients with any AE was 51.5% of lithium patients compared with 67.1% quetiapine.

Overall, the PBAC considered that the short duration of the trial precluded the possibility of concluding that lithium and quetiapine are non-inferior in terms of comparative safety.

9. Clinical Claim

The previous submission claimed quetiapine XR augmentation was superior to lithium augmentation in clinical effectiveness, which the PBAC considered was inadequately supported by the evidence presented. This re-submission has revised the clinical claim to non-inferiority versus lithium augmentation.

The PBAC recalled that in November 2011 it did not accept that quetiapine XR augmentation was equivalent in terms of comparative safety to lithium augmentation.

Based on the data presented in this re-submission, the PBAC did not consider that the claim of non-inferior comparative effectiveness and safety was adequately supported.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on a claim of non-inferiority. The November 2011 submission presented a cost-effectiveness model. The re-submission claimed that quetiapine XR 266 mg/day and lithium 900 mg/day are equi-effective.

The PBAC considered that the validity of the resubmission's economic results were affected by its reliance on results of one six-week open-label trial to indicate long-term constant efficacy in light of the lack of adequate follow-up and the missing data addressed by last

observation carried forward (LOCF). The PBAC also considered that insufficient evidence was provided to demonstrate the applicability of the RUBY trial to the proposed PBS population, particularly as the Product Information states that the usual effective daily dose is 150 mg, while RUBY used a dose of 300 mg/day.

Overall, the PBAC considered that the estimated dose relativity of quetiapine XR and lithium was not reliable as the submission appeared to apply different methodologies for calculating equi-effective doses for quetiapine and lithium. The PBAC noted also that approximately 50% of the patients in the RUBY trial did not achieve a lithium level in the target range, and considered that it was not appropriate to base an equi-effectiveness calculation on this dose.

The PBAC noted that the trials patients had more severe depression than would be expected in the Australian population, and that the effects of quetiapine in clinical practice may therefore be different to the results observed in the trial.

The submission estimated the costs of lithium therapy over the first year of treatment. The PBAC considered that this approach overestimated the number of blood tests for lithium, as patients will require more frequent tests during the first year of therapy until achieving stability. Once a patient's lithium therapy is stable the number of tests will taper to a level consistent with maintenance.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be more than 200,000 in Year 5, at an estimated net cost per year to the PBS of between $10 million -$30 million Year 5.

The PBAC noted that the following factors influencing the estimates of the patient population:

- The percentage of MDD patients treated with
- The percentage of patients who have failed first and second line treatment, as it is based on US data and may not be directly translatable to the Australian healthcare system..
- The percentage of TRD patients who receive augmentation treatment
- Uptake rate may be higher if quetiapine is favoured by patients due to reduced monitoring
- Potential leakage to patients who have failed only one antidepressant

The assumption that 25% of the estimated eligible patient population receives augmentation treatment was not justified by the re-submission, and the PBAC did not consider this to be reliable.

The re-submission assumed no market growth due to quetiapine XR augmentation for MDD and that it will replace only lithium augmentation treatment. The PBAC agreed that there may also be some substitution with antidepressants if used after failure of one antidepressant and in patients anticipated to fail the first or second treatment. The PBAC also considered it likely that there is some use of atypical antipsychotics in this setting already (i.e. outside the PBS restriction) and therefore the switch from lithium may not be as extensive as predicted.

The PBAC also agreed that the listing of quetiapine as augmentation therapy for treatment resistant depression may result in a perception that quetiapine is an antidepressant and therefore suitable for use earlier in the treatment algorithm, as an alternative to antidepressants. The PBAC did not accept that quetiapine will not displace antidepressants.

The PBAC considered the submission's estimates of savings to the MBS of reduced lithium monitoring costs compared with monitoring of quetiapine costs were overestimated.

The submission claimed an overall cost saving per year to Government of less than $10 million in Year 5.

The financial implications are to be further verified.

The PBAC considered that the submission's claimed overall cost saving would be unlikely to eventuate.

The submission proposed a weighting for the price of quetiapine in treatment resistant major depression. The PBAC noted that although the BEACH data presented in the pre-subcommittee response (PSCR) showed that 22% of existing quetiapine use is for depression, when non-PBS-subsidised indications of quetiapine are excluded from the BEACH data, 26.1% of quetiapine use is for depression. The PBAC therefore considered the proposed weighting to be low.

The PBAC noted data from the Drug Utilisation Sub-Committee (DUSC) Analysis of Antipsychotics that of patients initiating on quetiapine in current practice:

- 40% added quetiapine to an antidepressant
- 39% were not on an antidepressant just prior to initiating quetiapine
- 11% initiated quetiapine and an antidepressant at the same time; and
- 7.5% switched to quetiapine from an antidepressant.

The PBAC considered that a substantial proportion of patients initiating quetiapine without having been on an antidepressant immediately prior would not therefore meet the proposed PBS restriction. The PBAC considered also that the 51% of patients using quetiapine in combination with an antidepressant (either initiated simultaneously or sequentially) represented a population using a regimen, the initiation of which has little clinical place outside a hospital setting in the Australian healthcare system.

The PBAC noted also the high rate of utilisation of quetiapine in combination with an antidepressant in patients aged 20 to 59yrs, representing the population in which major depressive disorder is most frequently diagnosed.

The PBAC noted particularly the utilisation patterns of quetiapine 25 mg. The PBAC considered that there are few clinical indications for the initiation of a regimen of quetiapine plus an antidepressant outside a hospital setting. The PBAC also considered that quetiapine alone at a dose of 25 mg was likely to be sub-therapeutic for antipsychotic therapy and would therefore most plausibly be used for its hypnotic properties in the majority of patients. The PBAC reiterated its strong concerns about the clinical inappropriateness of these treatment

patterns. The PBAC considered that if these patterns were to apply to quetiapine 100 mg XR, the risk to patients of adverse events would be correspondingly higher at a higher dose.

Overall, the PBAC concurred with the DUSC that there is a high risk of quetiapine being used beyond the restriction, as an augmentation therapy added to the first antidepressant, or even as monotherapy. The PBAC considered that it is highly likely that utilisation of quetiapine would go substantially beyond simply substituting for lithium. DUSC analyses have shown that quetiapine prescribing patterns are inconsistent with those expected for the PBS listed indication schizophrenia and bipolar disorder. The PBAC did not consider it possible to establish whether an extension to the listing for quetiapine will promote further inappropriate use of quetiapine beyond current levels.

12. Recommendation and Reasons

The PBAC rejected quetiapine as augmentation for treatment resistant major depression on the basis that non-inferior comparative effectiveness and safety with the comparator, lithium, had not been established.

The PBAC considered that its concerns with the reliability of the key RUBY trial remained unresolved, particularly the lack of adequate follow up after the six week duration of the trial and the use of last observation carried forward to account for missing data.

With regard to the safety profile of quetiapine, the PBAC considered that the issue of weight gain with quetiapine, with 14 patients gaining more than 7% of their body weight over the six week duration of the RUBY trial, was cause for concern. The PBAC noted the potential flow-on health consequences of weight gain with regard to incidence of diabetes in younger patients most likely to be prescribed quetiapine for this indication.

The PBAC did not consider that the use of different methodologies to calculate equi-effective doses of quetiapine and lithium was appropriate. The PBAC also considered that as approximately half of the patients in the RUBY trial did not achieve adequate lithium levels at a dose of 900 mg per day, it was not appropriate to use this dose to calculate an equi-effective dose.

The PBAC considered that the cost offsets claimed in the resubmission were overestimated. In particular the PBAC did not accept the assumption that patients on lithium will have the same number of lithium tests in the first year of treatment as in subsequent years after stable therapy is achieved.

The PBAC noted that the resubmission's estimates of the patient population were underpinned by some assumptions that were not supported by the data, including the uptake rate of quetiapine among eligible patients. Overall, the PBAC did not consider the estimates of the eligible population to be reliable.

The PBAC noted and expressed concern over the utilisation patterns for quetiapine from the Drug utilisation Sub-Committee (DUSC) analysis of antipsychotics, particularly the use of low doses as potential hypnotics and the current use of quetiapine outside the proposed restriction for treatment resistant major depression in patients who have not been on two antidepressants prior to initiation. The use of quetiapine in combination with antidepressants

was also a matter of concern to the PBAC. Overall, the PBAC considered that there is high risk of use outside the proposed restriction.

The PBAC considered that a stakeholder meeting may help to provide context to the antipsychotic utilisation patterns observed in the DUSC analysis, particularly regarding prescribing patterns that may be regarded as unsafe. The PBAC requested that the Department liaise with relevant stakeholders to organise a meeting.

The PBAC referred the matter of antipsychotic prescribing patterns to the National Prescribing Service as the subject of a future education campaign.

Outcome:
Rejected

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 is working to correct some of the uncertainties surrounding the conclusions in the RUBY study so that the medical needs of the recurrent major depression population can be assisted by the PBS availability of quetiapine.