PUBLIC SUMMARY DOCUMENT
Product: Quetiapine, tablets (modified release), 50 mg, 150 mg, 200 mg, 300 mg and 400 mg (as fumarate), Seroquel XR®
Sponsor: AstraZeneca Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

The submission sought an extension to the current section 85 Authority Required (STREAMLINED) listing to include the treatment of resistant major depression (TRMD), as adjunctive therapy.

2. Background

Quetiapine modified release tablets had not been considered previously by the PBAC for TRMD.

3. Registration Status

Quetiapine modified release tablets were registered by the TGA 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)
As adjunctive therapy in treatment resistant major depression

For PBAC's view, see Recommendation and Reasons.

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 and 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. Patients who fail to respond to an adequate trial of first-line antidepressant therapy are described as having treatment resistant depression.

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 treatment resistant major depression (TRMD).

6. Comparator

The submission nominated lithium as the comparator.

The PBAC considered that although lithium was an appropriate comparator, electroconvulsive therapy (ECT) may also be considered.

7. Clinical Trials

The submission presented one open-label, randomised, 6-week trial (the RUBY trial) comparing quetiapine XR augmentation (add-on to current therapy), lithium augmentation and quetiapine XR monotherapy in patients with failed treatment response on one or two

antidepressant therapies. The quetiapine XR monotherapy arm was excluded from further review in the submission.

The primary outcome measure of the RUBY trial was change in total Montgomery-Asberg Depression Rating Scale (MADRS) score from randomisation to study end.

The RUBY trial was not published at the time of submission.

8. Results of Trials

Based on the results of the RUBY trial, the submission claimed that quetiapine XR augmentation demonstrated a small but statistically significant improvement in MADRS score compared to lithium augmentation.

The evaluation performed a post-hoc comparison of MADRS score changes between quetiapine and lithium, stratified by lithium plasma concentration, which suggested there was no statistical difference when the ITT population of the quetiapine XR augmentation group was compared to the subgroup of lithium augmentation patients who had achieved therapeutic levels of serum lithium by the end of the trial.

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

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials.

9. Clinical Claim

The submission claimed that quetiapine XR augmentation is superior in terms of efficacy and equivalent in terms of comparative safety over lithium augmentation.

The PBAC considered that the submission's claim that quetiapine XR augmentation is superior in terms of efficacy over lithium augmentation was inadequately supported by the evidence presented.

The PBAC did not accept the submission's claim that quetiapine XR augmentation was equivalent in terms of comparative safety to lithium augmentation.

10. Economic Analysis

The submission presented a stepped economic evaluation using a cost-utility analysis.

The submission's model was a Markov cohort model with weekly cycles and five treatment pathways: The model duration was 30 years.

The PBAC noted that while the model accounted for all-cause mortality, it did not account for excess mortality associated with major depression.

The outcomes used in the model were treatment efficacy (change in MADRS score), utilities, costs and QALYs.
The results of the analysis as presented in the submission produced a base case ICER of less than $15,000/QALY.

The submission presented a wide range of both univariate and multivariate sensitivity analyses, which all resulted in ICERs of less than $15,000.

The sensitivity analyses from the evaluation showed that the ICER increased to between $45,000 and $75,000/QALY. The PBAC considered that this analysis and variation in the estimated ICER demonstrated fundamental uncertainties in the model.

The Sponsor provided an amended respecified analysis in its Pre–Sub-Committee response which produced a higher ICER but was still less than $15,000/QALY. Notwithstanding the respecified analysis provided by the Sponsor, the PBAC was not confident in the estimates resulting from the model and therefore considered the ICER to be uncertain, but probably high.

11. Estimated PBS Usage and Financial Implications

The net financial cost/year to the PBS was estimated by the submission to be between $10 and $30 million in Year 5. The estimate was uncertain.

12. Recommendation and Reasons

The PBAC noted that the submission nominated lithium as the comparator for treatment resistant major depression (TRMD) as adjunctive therapy. Although lithium was considered an appropriate comparator, electroconvulsive therapy (ECT) may also be considered.

The PBAC noted that there is no universal consensus regarding the definition of TRMD. The clinical expert during the sponsor's hearing advised that the most generally accepted definition is failure of two antidepressant therapies. The PBAC considered that the requested restriction wording would allow use in a broad patient population, as no definition of TRMD is included. The PBAC noted that the pivotal trial presented in the submission (RUBY) included patients who had failed only one antidepressant, and therefore may not be representative of the requested PBS population, if the definition of TRMD of having failed two antidepressants is assumed.

From the results of the RUBY trial, the submission claimed that quetiapine XR augmentation demonstrated a small but statistically significant improvement in Montgomery-Asberg Depression Rating Scale (MADRS) score compared to lithium augmentation. However, the PBAC noted that the RUBY trial was designed as a non-inferiority trial, using the pre-defined non inferiority limit of 3 points on MADRS total score, and that the RUBY trial investigators considered the improvements not statistically significant at their pre-defined one-sided 97.5% confidence interval (modified intention to treat analysis).

The PBAC noted that three of the ten MADRS items are appetite, sleep and anxiety, and that treatment with quetiapine would give an automatic 30% improvement on the basis of its side effects of weight gain, sedation and somnolence. However, the PBAC did consider MADRS to be a reasonable score to use in this treatment setting. The results of an indicative post-hoc comparison performed during the evaluation suggested there was no statistical difference when the ITT population of the quetiapine XR augmentation group was compared to the subgroup of lithium augmentation patients who had controlled lithium levels.

The PBAC had additional concerns with the validity of the RUBY trial including the open-label nature of the trial, the subjective nature of outcomes using a depression scale completed

by clinicians, analysis based on modified intention to treat and an inadequate follow-up period of six-weeks treatment duration.

Overall, the PBAC considered that the submission's claim that quetiapine XR augmentation is superior in terms of efficacy over lithium augmentation was inadequately supported by the evidence presented.

In terms of safety, the PBAC observed the occurrence of specific adverse events was different between the two treatment arms. Given the differences in the adverse event profiles of the two drugs, the PBAC did not accept the submission's claim that quetiapine XR augmentation was equivalent in terms of comparative safety to lithium augmentation.

The submission presented a stepped economic evaluation using a cost-utility analysis. The base-case incremental cost per quality adjusted life year (QALY) was less than $15,000. However, the PBAC considered that there were several areas of economic uncertainty.

When a sensitivity analysis was done during the evaluation the ICER increased to between $45,000 and $75,000/QALY. The PBAC considered that this demonstrated the fundamental uncertainties in the model. The PBAC noted that the sponsor's alternative analysis produced an ICER higher than the original base case ICER but remained less than $15,000/QALY.

The PBAC therefore rejected the submission on the basis of inadequate clinical evidence to support a claim of superiority over the nominated comparator and therefore a cost-effectiveness analysis was not acceptable.

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 looks forward to working with the PBAC to make this medicine available for people with treatment resistant major depression.