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: July 2010

1. Purpose of Application

The submission requested the current Authority Required (Streamlined) listing for quetiapine immediate release and modified release tablets be simplified to "treatment of bipolar disorder". The submission also proposed an alternative listing for maintenance therapy as follows: "the monotherapy treatment of bipolar disorder with the addition of a mood stabiliser (lithium or sodium valproate) as clinically appropriate."

2. Background

Quetiapine (immediate release)
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. Listing was effective from 1 November 2000.

At the July 2007 meeting, the PBAC recommended extending the authority required PBS 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 for this indication was effective from 1 December 2007.

At the March 2009 meeting, the PBAC recommended extending the listing for quetiapine immediate release to include maintenance treatment of bipolar I disorder, in combination with lithium or sodium valproate. Listing was effective from 1 August 2009. At the same meeting, the PBAC rejected an application to extend the listing to include treatment of a patient with depressive episodes associated with bipolar disorder.

At the November 2009 meeting, the PBAC rejected submissions to (a) extend the listing for quetiapine immediate release to include treatment, for up to 6 months, of an episode of acute mania associated with bipolar I disorder, in combination with lithium or sodium valproate; and (b) extend the listing for quetiapine immediate release to include maintenance treatment of bipolar I disorder, as monotherapy.

Quetiapine (modified release)
At the July 2008 meeting, the PBAC recommended an authority required (Streamlined) listing for quetiapine modified release for the treatment of schizophrenia on a cost-minimisation basis against immediate release quetiapine on mg per mg basis.

At the November 2009 meeting, the PBAC recommended that quetiapine modified release tablets be listed with the same restrictions as the immediate release preparations for the treatment of bipolar I disorder on the basis of demonstrated efficacy in the treatment of acute mania and bipolar depression. Listing was effective from 1 April 2010.

3. Registration Status

Quetiapine fumarate immediate release and modified release tablets are TGA approved 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

Authority Required (Streamlined)

Treatment of bipolar disorder

or

The monotherapy treatment of bipolar disorder with the addition of a mood stabiliser (lithium or sodium valproate) as clinically appropriate.

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Bipolar I disorder is a psychiatric illness that is characterised by one or more manic, depressed or mixed episodes. The listing requested would allow treatment with quetiapine as monotherapy for the maintenance indication as well as combination therapy with lithium and sodium valproate.

6. Comparator

The submission nominated olanzapine as the main comparator.

For PBAC's view, see Recommendations and Reasons.

7. Clinical Trials

The submission presented as key evidence two randomised trials of treatments in patients with bipolar I disorder to form an indirect comparison of quetiapine and olanzapine with placebo as the common reference. Study 144 compares quetiapine at a maintenance dose of between 300 and 800mg/day compared with a placebo and lithium arm. Tohen 2006 compares olanzapine at a dose of between 5 and 20 mg/day with placebo. The key outcomes assessed in both trials were time to recurrence of a mood event of any type (manic/mixed/depressed).

Tohen 2005, was presented as supportive evidence. It assessed maintenance treatment of bipolar I disorder with olanzapine (dosed between 5 and 20 mg/day) as compared with lithium. The outcome of recurrence is numeric without a focus on the length of delay.

Details of the studies published at the time of submission are in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Tohen 2006	Randomised, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with	Am J Psychiatry 2006; 163: 247-256

	olanzapine.	
Tohen 2005	Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomised, double-blind, controlled clinical trial.	Am J Psychiatry 2005; 162: 1281-1290

8. Results of Trials

Comparative effectiveness

The key results of the two trials (Study 144 and Tohen 2006) incorporated in the submission's indirect comparison of quetiapine and olanzapine in time to recurrence of a mood event using interim intention to treat (ITT) population (patients for whom data was collected up to the interim stop date) and intention to treat (ITT) population (all randomised patients who received treatment) were as follows: Study 144 reported a significant advantage in time to recurrence of any type of event for quetiapine over placebo and likewise the Tohen 2006 trial of olanzapine reported a significant benefit for olanzapine over placebo in time to recurrence of any type of event.

The PBAC noted that there were three issues which reduced the comparability of the two trials used in the indirect comparison:

1. Structure of the trial. Both trials incorporated an open-label treatment stabilisation phase before the patients were randomised for the double-blind monotherapy maintenance treatment. Both trials saw a substantial number of withdrawals between enrolment and randomisation. This structure artificially selects a trial population that tolerates and responds to active treatment. The requested listing did not require patients to have been treated with quetiapine during its acute phase. The patient population who would get access to quetiapine under the proposed new PBS criteria may be more like the enrolment population of Study 144 and less like the randomised population. The inclusion criteria for Study 144 required that patients have had a past mood event within 26 weeks and have been treated with quetiapine continuously since. This criterion is applied pre-enrolment and there was still a large proportion of patients who did not make it to randomisation indicating that the quetiapine results may be overstated. A similar issue applies to the olanzapine trial.

2. Baseline demographics. The Tohen 2006 trial had a higher proportion of patients relative to Study 144 enrolled with rapid cycling bipolar I disorder (44.1-52.9% vs. 11.6-15.1%, respectively). These patients are recognised as more difficult to treat than patients without rapid cycling and as such this may have biased the results of an indirect comparison in favour of quetiapine. The submission addressed this by highlighting that, in Study 144, quetiapine had a significant effect over placebo for time to recurrence of any mood event regardless of rapid cycler status.

3. Differences in defining an acute manic and depression mood event. Both Study 144 and Tohen 2006 categorised a manic mood event using the Young Mania Rating Scale (YMRS) although Study 144 required two consecutive scores of ≥20 when Tohen 2006 required just one of ≥15. For categorising a depressed event Study 144 used the Montgomery-Asberg Depression Rating Scale (MADRS) requiring two consecutive scores of ≥20 while Tohen 2006 used the Hamilton Rating Scale for Depression (HAM-D) requiring one score of ≥15. The Tohen 2006 trial may have had a lower threshold for

classifying an event and, therefore, the indirect comparison could be biased against olanzapine.

Comparative toxicity

The PBAC noted that an indirect comparison between quetiapine and olanzapine using placebo as common reference in specific adverse events was not performed in the submission due to a lack of reported data in Tohen 2006 but considered the treatments similar in their adverse event profile. In terms of weight gain, both trials reported the percentage of patients who gained ≥7% of their body weight and, from an indirect comparison performed during evaluation, quetiapine was not found to be significantly different from olanzapine.

9. Clinical Claim

The submission claimed that quetiapine, based on the clinical evidence is non-inferior to, and non-interchangeable with, olanzapine in terms of efficacy and safety.

For PBAC's view, see Recommendations and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as 546mg/day of quetiapine ongoing as maintenance therapy and 12.5mg/day of olanzapine ongoing as maintenance therapy.

Using the current prices for the equi-effective doses of quetiapine and olanzapine, the submission estimated the difference in annual cost between quetiapine treatment and olanzapine treatment was less than $100 per patient per year. The submission used the difference between the estimated annual cost of quetiapine treatment and olanzapine as justification for a price increase.

For PBAC's view, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission assumed that quetiapine usage will likely be unaffected by any additional bipolar listing, with the exception of bipolar depression (which would be an additional population eligible under the broader PBS listing requested of "treatment of bipolar disorder" of less than 10,000 patients in Year 1 of listing).

The submission estimated the likely number of prescriptions dispensed per year to be between 10,000 and 50,000 in Year 4 of listing, for both bipolar I and II depression. Values for Year 5 were calculated during the evaluation, using the same methodology used in the submission to give a higher estimated number of prescriptions dispensed, while remaining in the range of 10,000 – 50,000 per year.

The submission estimated a net cost to the PBS of less than $10 million per year in Year 5. The submission's estimates were for the use in bipolar I and II depression. The submission assumed no financial impact for the proposed quetiapine listing for monotherapy maintenance treatment. No cost offsets for reduced treatments with olanzapine or mood stabilisers were considered in the submission.

For PBAC's view, see Recommendations and Reasons.

12. Recommendation and Reasons

The PBAC recommended extending the Authority Required (Streamlined) listing of quetiapine (as fumarate) 25 mg, 100 mg, 200 mg and 300 mg tablets and quetiapine (as fumarate) 50 mg, 200 mg, 300 mg and 400 mg tablets (modified release) on the PBS to include the maintenance treatment of bipolar I disorder as monotherapy on a cost minimisation basis with olanzapine tablets. The equi-effective doses are 546 mg of quetiapine (as fumarate) and 12.5 mg of olanzapine.

The PBAC considered olanzapine was an appropriate comparator, as it is the only atypical antipsychotic currently listed on the PBS for the maintenance treatment of bipolar 1 disorder as monotherapy.

The PBAC considered there was uncertainty in the claim of clinical non-inferiority based on the indirect comparison presented of study 144 and Tohen 2006, due to differences between the trials, including the different baseline populations and differences in the design of the trials. However the PBAC considered, on the basis of the evidence presented overall, that quetiapine is of non-inferior efficacy and safety to olanzapine for the maintenance treatment of bipolar I disorder, as monotherapy. The PBAC noted that no evidence was presented to support the broader listing requested of treatment of bipolar disorder and hence that the listing should be restricted to maintenance treatment of bipolar I disorder.

The PBAC considered that the utilisation estimates in the submission were uncertain, and the assumption in the submission that patients are already being treated with quetiapine for the maintenance of bipolar I disorder as monotherapy under the PBS outside the current restriction inappropriate. The PBAC hence did not accept that the listing of quetiapine for the maintenance treatment of bipolar I disorder as monotherapy would result in nil costs to the PBS. The PBAC also considered the submission's estimate of the number of prescriptions per year uncertain, as it was likely that the number for the higher strength of quetiapine were underestimated.

Recommendation:

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®

Amend the current restriction for use in bipolar I disorder as follows:

Restriction:	Authority Required (STREAMLINED) Schizophrenia; Monotherapy, for up to 6 months, of an episode of acute mania associated with bipolar I disorder; Maintenance treatment of bipolar I disorder.
Maximum quantity:	60 (25 mg, 50 mg, 200 mg, 300 mg and 400 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 is pleased with this recommendation and acknowledges that this is an important step toward securing ideal access to quetiapine for Australians with bipolar disorder.