PUBLIC SUMMARY DOCUMENT
Product: Ziprasidone hydrochloride, capsules 20 mg, 40 mg, 60 mg and 80 mg, Zeldox®
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: November 2008

1. Purpose of Application

The submission sought an extension of the current Authority Required (STREAMLINED) listing for ziprasidone to include monotherapy, for up to six months, of an episode of acute mania or mixed episodes associated with bipolar I disorder.

2. Background

This drug had not previously been considered by the PBAC for the treatment of bipolar I disorder.

At the November 2006 meeting, the PBAC recommended listing of ziprasidone for the treatment of schizophrenia on a cost-minimisation basis with olanzapine.

3. Registration Status

Ziprasidone hydrochloride was first registered by the TGA on 24 October 2001 for the treatment of schizophrenia and related psychoses, prevention of relapse and for maintenance of clinical improvement during continuation therapy. On 21 September 2006, the approved indications were extended to include monotherapy, for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Monotherapy, for up to 6 months, of an episode of acute mania or mixed episodes associated with bipolar I disorder.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Bipolar disorder (BPD, manic-depressive illness) is characterised by distinct episodes of mania and depression, with full inter-episode symptomatic recovery for most individuals. The clinical features of mania are elevated, expansive or irritable mood, accelerated speech, racing thoughts, increased activity and reduced sleep. Patients may develop grandiose ideas, act recklessly and show increased sexual drive and activity. When symptoms are less severe and of shorter duration, the term hypomania is used. Peak onset of illness is usually in early adult life and there is a strong genetic basis.

There are two types of BPD, type I defined as having at least one manic episode, with or without depressive episodes, and type II defined as hypomania and depression.

Ziprasidone is an atypical antipsychotic that will provide an alternative (when used as monotherapy) to currently available drugs to treat bipolar I disorder.

6. Comparator

The submission nominated olanzapine as the main comparator. The PBAC considered this appropriate.

7. Clinical Trials

The submission presented a meta-analysis of six randomised trials comparing ziprasidone with olanzapine (placebo and haloperidol as common comparators) in patients with BPD.

The trials and associated reports presented in the submission are presented in the table below.

Trial ID	Protocol title	Publication citation
Ziprasidone		
128-601	Ziprasidone in the treatment of acute bipolar mania: a 3 week, placebo controlled, double blind randomized trial. A phase III, randomized, placebo controlled study evaluating the safety and outcome of treatment with oral ziprasidone in subjects with mania.	Keck PE, Versiani M, Potkin S, et al Am J Psych, 2003; 160:741 8.
A1281083	Ziprasidone in acute bipolar mania: a 21 day randomised double blind, placebo controlled replication trial. A phase III, randomised, placebo controlled study evaluating the safety and outcome of treatment with oral ziprasidone in subjects with mania.	Potkin SG, Keck PE, Segal S, et al J Clin Psychopharmacol 2005; 25:301 10.
A1281052	Ziprasidone efficacy and safety in acute bipolar mania: 12 week study.	Ramey TS, Giller EL, Riesenberg R, et al Bipolar Disord 2005a; 7 (Suppl. 2): 89 (Abstract P193)
Olanzapine		
Tohen et al (1999)	Olanzapine versus placebo in the treatment of acute mania.	Tohen M, Sanger TM, McElroy SL, et al.Am J Psychiatry 1999; 156:702 9.
Tohen et al (2000)	Efficacy of olanzapine in acute bipolar mania.	Tohen M, Jacobs TG, Grundy SL, et al. Arch Gen Psychiatry 2000; 57:841 9.
Tohen et al (2003)	A 12 week, double blind comparison of olanzapine vs haloperidol in the treatment of acute mania.	Tohen M, Goldberg JF, Gonzalez Pinto AM, et al. Arch Gen Psychiatry 2003; 60:1218 26.

8. Results of Trials

The results for the primary outcome, change from baseline in (Young) Mania Rating Scale (Y/MRS), are presented below.

Mean change in Y/MRS from baseline of the indirect comparison – placebo and haloperidol as common comparator

	Ziprasidone			**Olanzapine**		
PLACEBO COMMON COMPARATOR						
Trial ID	**Diff (95% CI)**	**ZIP Mean change (SD)**	**PBO Mean change (SD)**	**OLZ Mean change (SD)**	**Diff (95% CI)**	**Indirect Diff (95% CI)**
128-601	-4.6 (-8.4, -0.9)	-12.4 (12.0)	-7.8 (12.9)			
A1281083	-5.5 (-8.5, -2.5)	-11.1 (11.5)	-5.6 (9.6)			

A1281052	-4.3 (-7.0, -1.7)	-10.4 (11.1)	-6.1 (9.9)			
Tohen 1999			-4.9 (11.6)	-10.3 (13.4)	-5.4 (-9.6, -1.2)	
Tohen 2000			-8.1 (12.7)	-14.8 (12.5)	-6.7 (-11.4, -1.9)	
Pooled REM	**-4.8 (-6.5, -3.0)**				**-5.9 (-9.1, -2.8)**	**1.2 (-2.4, 4.8)**
Network meta-analysis					**2.5 (-0.3, 5.3)**	
HALOPERIDOL COMMON COMPARATOR						
Trial ID	**Diff (95% CI)**	**ZIP Mean change (SD)**	**HAL Mean change (SD)**	**OLZ Mean change (SD)**	**Diff (95% CI)**	**Indirect Diff (95% CI)**
A1281052	5.5 (3.2, 7.8)	-10.4 (11.1)	-15.9 (10.6)			
Tohen 2003			-23.5 (10.8)	-21.3 (11.0)	2.2 (0.2, 4.2)	3.3 (0.3, 6.4)

Abbreviations: ZIP ziprasidone, HAL haloperidol, OLZ olanzapine, PBO placebo; REM random effects method; CI confidence interval; Y/MRS Young/ Mania Rating Scale

The changes from baseline in Y/MRS scores for placebo were similar (5-8 points) across the ziprasidone versus placebo and the olanzapine versus placebo trials. Both ziprasidone and olanzapine resulted in a statistically significant difference in change from baseline in Y/MRS scores compared to placebo. The indirect comparison of ziprasidone and olanzapine showed no significant difference in change from baseline in Y/MRS 1.2 (95% CI: -2.4, 4.8). The minimum clinically important difference for the Y/MRS rating scale is of the order of 3-5 points.

The changes from baseline Y/MRS scores for haloperidol were not similar (16, 24 points) across the ziprasidone versus haloperidol and the olanzapine versus haloperidol trials. Both ziprasidone and olanzapine resulted in a statistically significant difference in change from baseline in Y/MRS scores compared to haloperidol. The indirect comparison of ziprasidone and olanzapine showed a significant difference in favour of olanzapine 3.3 (95% CI: 0.3, 6.4) but this is not likely to be clinically important. The PBAC noted that haloperidol was superior to both ziprasidone and olanzapine for change from baseline in Y/MRS scores.

A network meta-analysis (which combines the data from the placebo and haloperidol controlled trials for the primary outcome) showed no statistically significant difference between olanzapine and ziprasidone in change from baseline in Y/MRS scores (2.5 [95% CI: -0.3, 5.3).

The most common adverse events with ziprasidone (occurring more frequently than with placebo) were somnolence, dizziness, hypertonia, akathisia, extrapyramidal syndrome (EPS), and dystonia. The most common adverse events with olanzapine (that were more frequent than with placebo) were somnolence, dry mouth, dizziness, and asthenia. Ziprasidone was associated with more EPS, whereas olanzapine was associated with more weight gain and somnolence. The submission noted that, overall, the AE burden was considered to be of a similar magnitude with both agents.

9. Clinical Claim

The submission described ziprasidone as equivalent in terms of comparative effectiveness and similar in terms of comparative safety over olanzapine.

10. Economic Analysis

The submission presented a cost minimisation analysis. The PBAC accepted the equi-effective doses of ziprasidone 119.85 mg daily and olanzapine 15.19 mg daily (risperidone 5.4 mg daily).

11. Estimated PBS Usage and Financial Implications

The submission estimates that the requested listing will not increase the current market as it assumes that ziprasidone will substitute for other agents. The likely number of prescriptions dispensed per year in year 5 was estimated in the submission to be between 10,000 and 50,000. The total cost of ziprasidone was estimated at less than $10 million in year 5.

12. Recommendation and Reasons

The PBAC recommended an extension to the listing for ziprasidone to include the treatment of acute mania or mixed episodes associated with bipolar disorder I on a cost-minimisation basis with olanzapine and recommended that the equi-effective doses are ziprasidone 119.85 mg and olanzapine 15.19 mg daily (risperidone 5.4 mg daily).

The PBAC noted that the submission proposed a weighting to the indications bipolar I to schizophrenia and that the Pharmaceutical Benefits Pricing Authority (PBPA) would need to determine the appropriate weighting between the two indications.

The PBAC agreed that the indirect comparison between olanzapine and ziprasidone using placebo as a common comparator was acceptable. The PBAC noted that the changes from baseline in Young/ Mania Rating Scores (Y/ MRS) for placebo were similar (5-8 points) across the ziprasidone versus placebo and the olanzapine versus placebo trials. Both ziprasidone and olanzapine resulted in a statistically significant difference in change from baseline in Y/ MRS scores compared to placebo. The indirect comparison of ziprasidone and olanzapine showed no significant difference in change from baseline in Y/MRS 1.2 (95% CI: -2.4, 4.8). The minimum clinically important difference for the Y/MRS rating scale is of the order of 3-5 points.

The PBAC noted that it would be difficult to restrict the use of ziprasidone to 6 months and that there was also potential for use outside the listing criteria due to the Streamlined Authority listing.

The PBAC noted that there was inconsistency in the wording of the restrictions for quetiapine, olanzapine and ziprasidone and that although the restriction wording specified use as monotherapy for ziprasidone and quetiapine, lithium was recommended for use in conjunction with the atypicals. The PBAC agreed to review the restriction wording at a future date.

Recommendation

ZIPRASIDONE, capsule, 20 mg, 40 mg, 60 mg and 80 mg

Restriction: Authority Required (STEAMLINED)
Monotherapy, for up to 6 months, of an episode of acute mania or mixed episodes associated with bipolar I disorder

Maximum quantity:	60	(all strengths)
Number of repeats:	5	(all strengths)

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

Pfizer Australia welcomes the PBAC recommendation for ziprasidone (Zeldox®) to be listed on the PBS. The Sponsor believes the availability of Zeldox® will provide an important additional management option for individuals with acute mania and mixed episodes associated with bipolar I disorder. As part of Pfizer Australia's ongoing commitment to the appropriate use of our medicines we look forward to the continued implementation of the Quality Use of Medicine programme for Zeldox®, the details of which were provided in this application to the PBAC.