PUBLIC SUMMARY DOCUMENT

Product: Ziprasidone Hydrochloride, capsules, 20 mg, 40 mg, 60 mg, 80 mg, Zeldox®

Sponsor: Pfizer Australia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission requested an Authority Required PBS listing for the treatment of schizophrenia.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Ziprasidone hydrochloride was 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.

4. Listing Requested and PBAC's View

Authority required
Schizophrenia.

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

Ziprasidone hydrochloride belongs to the new generation of antipsychotic drugs known as 'atypical' agents. The 'atypical' drugs have shown advantages over the older 'typical' agents with improved usefulness against negative symptoms of schizophrenia, a decreased incidence of extrapyramidal syndrome (EPS) and are better tolerated.

6. Comparator

The submission nominated olanzapine as the main comparator. The PBAC considered this as appropriate, however noted that a comparison of ziprasidone and risperidone would have also been informative.

7. Clinical Trials

The submission presented four randomised head-to-head studies directly comparing ziprasidone and olanzapine.

Three of these studies were published at the time of submission, as follows:

Trial/First author	Protocol title	Publication citation
BREIER (2005) Breier, A et al	Olanzapine versus ziprasidone: results of a 28-week double blind study in patients with schizophrenia.	Am J Psychiatry 162: 1879-1887
STUDY – 0548 Simpson, G et al (2004)	Randomised, controlled double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder.	Am J Psychiatry 161: 1837-1847
Harvey, P (2003)	Ziprasidone and Cognition: the evolving story.	J Clin Psychiatry 64 (Suppl 19): 33-39
Harvey, P et al (2004)	Randomised, controlled double-blind multicenter comparison of the cognitive effects of ziprasidone versus olanzapine in acutely ill patients with schizophrenia or schizoaffective disorder.	Psychopharmacology 172: 324-332
Glick, I et al	Ziprasidone's benefit versus olanzapine regarding weight and insulin resistance.	Eur Neuropsychopharmacol 11 (Suppl 3): S273, Abstract P.2.070.
STUDY – 0548/-0570 (24 week extension phase of Study – 0548) Simpson, G et al (2005)	Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia	Am J Psychiatry 162: 1535-1538.
Harvey, P et al (2006)	Neuropsychological normalisation with long-term atypical antipsychotic treatment: results of a six-month, randomised, double-blind comparison of ziprasidone and olanzapine,	J Neuropsychiatry Clin Neurosci 18: 54-63

8. Results of Trials

The primary outcomes of the four head-to-head trials are change from baseline in the Clinical Global Impression of Severity (CGI-S) and change from baseline in the Positive and Negative Syndrome Scale (PANSS) Total scores.

The trial results for change from baseline in CGI-S and PANSS score showed that olanzapine had a small statistically significant, but probably clinically undetectable, benefit over ziprasidone in the pooled analysis for the intention to treat (ITT) population. There was no statistically significant difference between ziprasidone and olanzapine in the pooled analysis for the completer population.

Response rates were defined as primary outcomes in three of the four key studies, however results on this measure were not presented in the submission. Data extracted during evaluation of the submission demonstrated that olanzapine had statistically significantly better response rates in two studies at a threshold of 20% and 30% improvement in PANSS

Total scores, but there was no difference between ziprasidone and olanzapine at the 40% level of reduction in PANSS score.

Discontinuation rates in the studies were higher for ziprasidone than olanzapine with the main reasons attributed to adverse events, and ziprasidone being initiated at too low doses with resulting lack of efficacy.

Ziprasidone was associated with a higher occurrence of back and chest pain, nausea, vomiting, akathisia and insomnia. Olanzapine was associated with a higher incidence of weight gain and had a consistently greater adverse impact on metabolic profile (cholesterol, triglycerides and diabetogenic effects as measured by glucosylated haemoglobin (HbA1c). Both olanzapine and ziprasidone produced similar changes in QTc interval which were not statistically significantly different. *For PBAC's comments on these results, see Recommendation and Reasons.*

9. Clinical Claim

The submission described ziprasidone as being no worse than olanzapine in terms of effectiveness and toxicity.

10. Economic Analysis

A preliminary economic evaluation was presented using a cost-minimisation approach. This was considered valid by the PBAC. The resources included were drug costs.

The equi-effective doses in the context of cost-minimisation were ziprasidone 120.30 mg/day and olanzapine 14.38 mg/day.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 4 of listing the likely number of patients would be in the range 50,000 – 100,000 for all atypical agents and the financial cost to the PBS (excluding co-payments) would be < $10 million.

12. Recommendation and Reasons

The PBAC recommended listing on a cost minimisation basis with olanzapine at the price proposed in the submission, acknowledging that this price is lower than that which would be obtained using the trial-based equi-effective doses of the two drugs.

The PBAC was concerned that based on the clinical trial evidence presented, the efficacy of ziprasidone may be lower than olanzapine. Of particular concern was the statistically significantly higher response rate in the intent to treat population in Trial 002 for olanzapine over ziprasidone in the percentage of patients achieving a 30% or greater reduction in PANSS Total score. The other statistically significantly observed differences between olanzapine and ziprasidone in PANSS and CGI severity scores were considered not to be clinically relevant. The Committee accepted the argument presented in the Pre-PBAC Response and at the hearing that this difference may be due to ziprasidone being initiated at too low doses in the clinical trials as evidenced by the high withdrawal rates due to lack of efficacy. The

Committee further considered that the possibility of reduced efficacy with ziprasidone would be offset by the weight gain benefit observed with ziprasidone over olanzapine. There was no statistically significant difference between ziprasidone and olanzapine in the pooled analysis for the completer population.

The equi-effective doses based on the clinical trials are ziprasidone 120.30 mg/day and olanzapine 14.38 mg/day.

In order to address the uncertainties about the doses of ziprasidone that will be used in practice as well as the dose of olanzapine, the Committee recommended to the PBPA that the atypical antipsychotics could be considered for inclusion in the WAMTC process (Weighted Average Monthly Treatment Cost) with ziprasidone, olanzapine and aripiprazole included in one WAMTC group and risperidone, quetiapine and amisulpride in a second WAMTC group.

The PBAC recommended the 20 day safety net rule should not apply.

Recommendation
Ziprasidone Hydrochloride, capsules, 20 mg, 40 mg, 60 mg, 80 mg

Restriction:	Authority required Schizophrenia.
Maximum quantity:	60
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

As noted in the PES Commentary, the studies employed different dose ranges for ziprasidone some of which were outside (below) the ranges recommended. In light of what is known about initial dosing for ziprasidone this is an important factor to consider in interpreting the study results.