PUBLIC SUMMARY DOCUMENT
Product: PALIPERIDONE, prolonged release tablets, 3mg, 6 mg, 9 mg, 12 mg, Invega®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application
The submission sought a Section 85 Authority required (Streamlined) listing for schizophrenia.

2. Background
This drug had not previously been considered by the PBAC.

3. Registration Status
Paliperidone's TGA registration commenced on 17 September 2007. Paliperidone prolonged release tablets are indicated for the treatment of schizophrenia, including acute treatment and recurrence prevention.

4. Listing Requested and PBAC's View
Authority required (Streamlined)
Schizophrenia

The PBAC had no comments on the requested restriction wording.

5. Clinical Place for the Proposed Therapy
Paliperidone prolonged release is a once daily oral atypical antipsychotic medication for the treatment of schizophrenia.

6. Comparator
The submission appropriately nominated olanzapine as the main comparator.

7. Clinical Trials
The submission presented four pivotal, head-to-head trials of paliperidone and olanzapine in patients with schizophrenia and experiencing an acute attack: three of the trials employed a fixed dosing regimen (Kane et at (2007), Marder et al (2007) and Davidson et al (2007)) and the remainder a flexible dosing regimen for 6 weeks (dose range: paliperidone 3-12 mg/day and olanzapine 5-15 mg/day, unpublished study). Nine supportive trials were presented: one placebo-controlled flexible dose trial in patients ≥65 years, one placebo-controlled flexible dose trial in relapse prevention, five open label extension studies (being open-label single-arm paliperidone extensions of the three pivotal head-to-head fixed dose and two supportive placebo controlled flexible dose trials), one cardiovascular safety trial and one sleep architecture trial. One pooled analysis of the three pivotal fixed dose trials was also presented.

The trials published at the time of submission are as follows:

Trial/First author	Protocol title	Publication citation
Pivotal direct randomised trials		
Kane et al 2007	Treatment of schizophrenia with paliperidone extended-release tablets: A 6-week placebo-controlled trial.	Schizophr Res; 90 (1-3):147 – 61.
Marder et al 2007	Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomised, placebo-controlled study.	J.Biopsych (E-publication ahead of print)
Davidson et al 2007	Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): Results of a 6-week, randomised, placebo-controlled study.	Schizophrenia Research 93; 93: 117-130.c
Supportive trials and studies		
Kramer 2007	Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: A randomised, double-blind, placebo-controlled study.	Journal of clinical psychopharmacology 27(1):6-14.

8. Results of Trials

The pooled results for paliperidone versus placebo from the key fixed-dose trials are summarised in the table below:

Trial	Change from baseline total PANSS score – mean (SD)				
	Placebo	**Pali 3 mg/day**	**Pali 6 mg/day**	**Pali 9 mg/day**	**Pali 12 mg/day**
Kane et al 2007	N = 126 -4.1 (23.16)		N = 123 -17.9 (22.23)	N = 122 -17.2 (20.23)	N = 129 -23.3 (20.12)
Marder et al 2007	N = 105 -8.0 (21.48)		N = 110 -15.7 (18.89)		N = 111 -17.5 (19.83)
Davidson et al 2007	N = 120 -2.8 (20.89)	N = 123 -15.0 (19.61)		N = 123 -16.3 (21.81)	
Pooled analysis					
N	351	123	233	245	240
Baseline	93.9 (11.68)	91.6 (12.19)	93.4 (11.22)	93.6 (12.55)	94.4 (11.16)
Week 6	-4.8 (21.95)	-15.0 (19,61)	-16.9 (20.70)	-16.8 (21.00)	-20.6 (20.15)

PANSS = Positive and Negative Syndrome Scale

The submission provides unpublished pooled analyses of different doses of paliperidone versus olanzapine from the three fixed dose trials. The results of these analyses for change from baseline in total PANSS score showed no significant differences between any dose of paliperidone and olanzapine. However, the primary comparison in each of the trials was between each paliperidone group and placebo, and as such, the trials may not have been powered to detect any differences between paliperidone and olanzapine.

An unpublished non-inferiority trial comparing paliperidone and olanzapine was presented. The non-inferiority limit of the trial, as specified in the protocol was 7 points in the total PANSS scores. The upper limit of the 95% confidence interval for the differences between the two treatment groups indicated that the non-inferiority criteria

had been met and the results indicated that paliperidone is non-inferior to olanzapine for the outcome of change in total Positive and Negative Syndrome Scale (PANSS) score at 6 weeks.

The PBAC agreed that the sponsor's argument in support of a 7 point difference in PANSS as a clinically unimportant difference for non-inferiority was reasonable. Overall, the confidence intervals around the treatment differences in the four key trials are reasonably narrow suggesting that paliperidone is non-inferior to olanzapine at the doses used in the trials.

In terms of comparative toxicity, the pooled analysis indicated that the occurrence of serious adverse events was comparable across all treatment groups. Metabolic system adverse events (body weight increase ≥ 7%, triglyceride abnormality), occurred in a statistically significantly greater proportion of patients treated with olanzapine compared with paliperidone in the pooled analysis. Nervous system adverse events (akathisia and any EPS syndrome) occurred in a statistically significantly greater proportion of patients treated with paliperidone compared with olanzapine.

For the PBAC's comments on these results, see *Recommendation and Reasons.*

9. Clinical Claim

The submission claimed that paliperidone is non-inferior to olanzapine in terms of efficacy and safety. The dose relativity between paliperidone and olanzapine was claimed to be 1:1.31 mg.

For the PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

A trial-based economic evaluation was presented. The choice of a cost-minimisation approach was considered valid. The resources included were drug costs only. The submission calculated that the drug cost per patient per year was less than $15,000 for both paliperidone and olanzapine.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of scripts/year to be in the range of 100,000 – 200,000 by Year 5.

The submission estimated financial savings/year to the PBS (excluding co-payments) of up to $1 million over 5 Years. The overall market is not expected to grow or to grow more rapidly as a result of listing paliperidone.

12. Recommendation and Reasons

The PBAC recommended the listing of paliperidone on the PBS for schizophrenia on a cost-minimisation basis compared with olanzapine and that the equi-effective doses were paliperidone 9.83mg per day and olanzapine 12.91mg per day.

The PBAC considered that paliperidone is non-inferior to olanzapine in the PANSS score at 6 weeks as the score was below the non-inferiority limit of 7 points.

The PBAC noted that there was a statistically significant difference between paliperidone and olanzapine for weight gain (favouring paliperidone) and the incidence of extrapyramidal symptoms (EPS) (favouring olanzapine).

Based on the supporting data, despite accepting the clinical claim, the PBAC considered there was some uncertainty with respect to the claim that paliperidone was no worse than olanzapine in terms of effectiveness and having quantitatively similar, but different toxicity profile. This was because the dosing of olanzapine may have been suboptimal and there was uncertainty regarding whether the patients enrolled in the trials forming the primary source of evidence in the submission are representative of those for whom PBS listing is sought, as the patients enrolled in the trials were experiencing an acute attack.

The PBAC noted that the pivotal trials were all of 6 weeks duration, and considered that the data may only represent equi-effectiveness of paliperidone and olanzapine in the acute phase, however listing is requested for both the acute and maintenance phases of the disease.

The PBAC noted that a flat pricing structure was proposed and recommended a risk share agreement be put in place.

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

The sponsor welcomes the decision by the PBAC to recommend listing of an additional treatment option for patients with schizophrenia.