PUBLIC SUMMARY DOCUMENT
Product: Paliperidone palmitate, aqueous suspension for injection, 25 mg, 50 mg, 75 mg, 100 mg and 150 mg, pre-filled syringe, Invega® Sustenna™
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application
The submission sought an Authority Required (Streamlined) listing for the treatment of schizophrenia.

2. Background
This injectable preparation of paliperidone had not previously been considered by the PBAC.

At its November 2007 meeting, the PBAC recommended the listing of paliperidone tablets on the PBS for schizophrenia on a cost-minimisation basis compared with olanzapine. The equi-effective doses were paliperidone 9.83 mg per day and olanzapine 12.91 mg per day. Paliperidone 3, 6 and 9 mg tablets were listed on 1 April 2008. The 12 mg tablet was listed on 1 October 2008 and deleted from the PBS on 1 December 2009.

3. Registration Status
Paliperidone palmitate aqueous suspension for injection, 25 mg, 50 mg, 75 mg, 100 mg and 150 mg were TGA registered on 28 July 2010 for the acute and maintenance treatment of schizophrenia in adults.

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

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy
Schizophrenia is a chronic and severe psychiatric illness characterised by disturbances in speech, perception, cognition, volition and emotion.

The submission claimed that paliperidone injection would provide an alternative atypical antipsychotic depot injection to risperidone and olanzapine for the treatment of schizophrenia.

6. Comparator
The submission nominated risperidone modified release injection as the main comparator, on the basis that it is the most commonly prescribed long acting atypical antipsychotic injection on the PBS.

The PBAC agreed that this was the appropriate comparator as it is the product most likely to be replaced in clinical practice if the decision to use a depot formulation is made.

7. Clinical Trials
The submission presented two direct randomised trials comparing paliperidone long acting injection (LAI) with risperidone LAI treatment in patients aged ≥18 years, with schizophrenia

for ≥1 year and a total Positive and Negative Syndrome Scale (PANSS) score of 60−120 at baseline. Trial PSY-3006 (double-blind, double-dummy, 78% European, 22% US) was used as primary evidence and Trial PSY-3008 (open-label, 100% Chinese) was used as supportive evidence. The studies were not yet published at the time of the submission.

8. Results of Trials

The primary outcome of the trials was change in PANSS total scores from baseline to endpoint. The non-inferiority margin was defined as −5 points in Trial PSY-3006 and −5.5 points in Trial PSY-3008.

There were no statistically significant differences between paliperidone LAI and risperidone LAI in change in PANSS total score from baseline in either trial except for the intention-to-treat (ITT) analysis in Trial PSY-3008 where the results of the ITT analysis favoured risperidone LAI.

For Trial PSY-3006, paliperidone LAI was non-inferior to risperidone LAI as the lower bound of the 95% CI for the difference in mean change in PANSS total scores was greater than −5 points.

For Trial PSY-3008, paliperidone LAI was non-inferior to risperidone LAI as the lower bound of the 95% CI for the difference in mean change in PANSS total scores was greater than −5.5 points. The submission argued that the lower bound of the 95% CI in the ITT analysis was bordering the 7-point difference previously accepted by the PBAC as a clinically unimportant difference.

In Trial PSY-3006, the most common Treatment Emergent Adverse Events (TEAE) were insomnia, headache, somnolence and injection site pain in the paliperidone LAI group and insomnia and headache in the risperidone LAI group. In Trial PSY-3008, akathisia and tremor were also common.

There was a significantly increased risk of possibly drug-related adverse events, 'psychiatric disorders' including anxiety, and 'general disorders and administration site conditions' including injection site pain with paliperidone LAI treatment in Trial PSY-3006. In Trial PSY-3008 there were more nervous system disorders reported for risperidone LAI compared with paliperidone palmitate LAI primarily due to a significantly greater incidence of tremor reported in the risperidone group.

In the direct clinical trials, injection site pain was reported in a small proportion of patients.

The submission reported that no additional safety issues were identified in the first Periodic Safety Update Report (PSUR) for paliperidone LAI or in the most recent PSUR for oral paliperidone.

No data on the effects of long-term exposure to paliperidone palmitate were presented in the submission.

9. Clinical Claim

The submission claimed that paliperidone LAI is superior in terms of overall effectiveness (non-inferior in clinical trial end-points but superior in actual clinical practice) and similar in terms of safety over risperidone LAI.

The PBAC considered that based on the evidence presented, the claim of superiority in clinical practice was not justified.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission's approach to calculating dose relativity is summarised below

Issue	Results
Dose relativity in actual clinical practice • The weighted final doses in Trial PSY-3006 represent mean doses for 'non-steady state' patients; • dose relativity using weighted dose at study endpoint: 1 mg risperidone LAI: 1.76 mg paliperidone LAI	• Weighted average dose of paliperidone LAI based on post-launch US sales data in April 2010 was used as proxy for weighted average dose of paliperidone LAI in actual clinical practice in Australia • Weighted average dose of risperidone LAI was based on scripts processed through Medicare Australia in April 2010 • The dose relativity in actual clinical practice in Australia was proposed as 1 mg risperidone LAI: 1.32 mg paliperidone LAI

The submission stated that in the clinical trials patients commenced treatment in a non-steady state due to the wash out period and thus patients only achieved an on-treatment steady state with paliperidone LAI at Day 8 because they had received the loading dose of 150 mg and 100 mg on Day 1 and Day 8, respectively. The clinical trials thus do not capture patients who switch therapies in the steady state condition and hence commence at a dose based on a 1:1 ratio. Therefore, the submission concluded that an overall average dose (and dose-relativity) for paliperidone palmitate LAI and risperidone LAI that reflects both the non-steady-state and steady state patients is required.

The submission also calculated cost-offsets associated with the decreased frequency of injection.

Consistent with a claim of superiority, the submission originally presented a stepped economic evaluation versus risperidone LAI as the primary analysis and a cost comparison versus olanzapine LAI as a secondary analysis. The type of economic evaluation presented was a cost-utility analysis.

However, following advice from the PBAC's Economics Sub-Committee (ESC), the sponsor presented a cost-minimisation analysis which accounted for differences in administration costs and oral antipsychotic supplementation requirements. The PBAC agreed that this was more appropriate than the cost-utility analysis originally presented in the submission. *See Recommendation and Reasons.*

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be less than 10,000 in year 5. This was considered a likely underestimate.

Based on the original cost-effectiveness approach, the submission estimated the net cost per year to the PBS to be less than $10 million in year 5. Revised estimated net costs based on the cost-minimisation approach were not provided.

12. Recommendation and Reasons

The PBAC recommended the listing of paliperidone palmitate LAI on the PBS as an Authority Required (Streamlined) listing for the treatment of schizophrenia on a cost-minimisation basis compared with risperidone modified release injection. The pragmatic dose relativity accepted by the PBAC for pricing purposes was 1:1.32 for injected risperidone and injected paliperidone, respectively, based on USA sales and Medicare data. In view of the uncertainty regarding the dose relativity, the PBAC considered that this dose relativity should be reviewed in 12 months time based on PBS data. For pricing purposes, the PBAC agreed that there could also be an offset for the use of oral risperidone during titration of injected risperidone due to its 3-week lag of onset of effect, as well as for the administration of an extra dose of injected risperidone every four weeks, given it is administered fortnightly whereas paliperidone is administered once every four weeks.

The PBAC agreed that risperidone modified release injection was the appropriate comparator as it is the product most likely to be replaced in clinical practice if the decision to use a depot formulation is made.

The PBAC considered that the results of trials PSY-3006 and PSY-3008 suggest no statistically significant differences between paliperidone LAI and risperidone modified release injection in the primary outcome of change in PANSS total score from baseline, and in the secondary outcomes assessed. The PBAC noted that there were differences in dosing frequencies between paliperidone and risperidone in the trials (4-weekly versus 2-weekly).

The PBAC noted the sponsor's proposal in its pre-PBAC response to present a cost-minimisation analysis following the advice of the ESC, including accounting for differences in administration costs and oral antipsychotic supplementation requirements. The PBAC agreed that this was more appropriate than the cost-utility analysis presented in the submission.

The PBAC considered the main issues relating to the cost-minimisation approach to be the determination of dose relativity and cost-offsets due to reduced administration costs with less frequent dose administration, and there being no requirement for oral supplementation with paliperidone compared with risperidone during the initiation phase (as noted in the clinical trials presented).

The PBAC noted that determining the equi-effective doses based on the doses being used at the end of clinical trial data for the population of patients switching from oral antipsychotics would not include the impact of the need for a loading dose. The washout period may also not have been adequate for patients who were already on long acting injections. The PBAC agreed that the trial data were not at steady state and were immature. Therefore, the dose

relativity of 1:1.76 for injected risperidone to injected paliperidone at study endpoint may not be informative of the equi-effective doses in this instance.

The PBAC also accepted the submission's argument that, based on the paliperidone product information, the population of patients switching from injected risperidone to injected paliperidone would do so on a 1:1 dose relativity basis. The PBAC noted that the submission provided no basis to weight the different dose relativities across the two populations determined by what product patients were receiving before starting injected paliperidone.

The PBAC further noted the paliperidone dose from USA sales data was similar to that at the end of the trial. The average dose of risperidone at the end of the trial was less than both the USA sales data and the Australian Medicare data. The PBAC considered that the difference in dose relativities provided in the submission appeared to be driven by the injected risperidone dose in the trial compared with those obtained from the utilisation data.

Overall, the PBAC agreed that, in this instance, the proposed dose relativity of 1:1.32 based on USA sales and Australian Medicare data may be a more pragmatic basis for determining a dose relativity for pricing purposes, noting that it lies between the two estimates for the two populations and because it also represents an approximation of the steady state dose. This pragmatic approach was agreed due to the inadequacies of the usually preferred trial basis for determining equi-effective doses for patients switching from oral antipsychotics, and the inability to estimate the relative proportions of the two populations to determine a weighting for an evidence-based estimation of equi-effective doses.

Regarding the cost-offsets, the submission calculated a cost-offset per risperidone modified release injection avoided, using a sponsor commissioned survey which took into account labour costs and travel time. The PBAC considered the usual method of determining cost-offsets to account for administration costs is to use a Medicare schedule fee for the extra consultation every four weeks, and in this case a Level B consultation fee was deemed appropriate.

The PBAC noted the consumer comments received for this item.

Recommendation:
PALIPERIDONE PALMITATE, aqueous suspension for injection, 25 mg, 50 mg, 75 mg, 100 mg and 150 mg, pre-filled syringe

Restriction:	Authority Required (STREAMLINED) Schizophrenia
Maximum quantity:	1
Repeats:	5

NOTE:
Shared Care Model:
For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further

information can be found in the Explanatory Notes for Nurse Practitioners.

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

Janssen-Cilag welcomes this recommendation by the PBAC to provide access to a new long-acting injectable treatment option for Australian schizophrenia patients.