

5.10 PALIPERIDONE
Injection, 175, 263, 350, 525 mg
Invega® Trinza™
Janssen-Cilag Pty Ltd.

1 Purpose of Application

1.1 Authority Required (STREAMLINED) listing for PP3M long acting injectable (LAI) antipsychotic for treatment of patients with schizophrenia who have been adequately treated with Paliperidone one month LAI for at least four months.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PALIPERIDONE PALMITATE				
Aqueous solution for injection, 273mg, prefilled syringe	1	1	\$ [REDACTED]	
Aqueous solution for injection, 410mg, prefilled syringe	1	1	\$ [REDACTED]	Invega® Janssen-Cilag Pty Trinza™ Ltd.
Aqueous solution for injection, 546mg, prefilled syringe	1	1	\$ [REDACTED]	
Aqueous solution for injection, 819mg, prefilled syringe	1	1	\$ [REDACTED]	
Category / Program	GENERAL – General Schedule (Code GE)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Condition:	Schizophrenia			
PBS Indication:	Schizophrenia			
Treatment phase:	initial			
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined			
Clinical criteria:	<i>Patient must have previously received and be stabilised on PBS-subsidised paliperidone once-monthly injection for at least 4 consecutive months.</i> Patient must be stabilised on paliperidone palmitate once-monthly formulation for at least 4 months.			
Prescriber Instructions	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.
Administrative Advice	<p><i>Patient dosage is to be determined as per the dose transition table in the Product Information based on the maintenance dose of paliperidone once-monthly injection.</i></p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p>

2.2 The listing was requested on a cost-minimisation basis compared with PP1M LAI.

For more detail on PBAC's view, see section 7 "PBAC outcome".

3 Background

3.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration paliperidone 3-month LAI presentations (175 mg, 263 mg, 350 mg and 525 mg) were TGA registered (as of 23 September 2016).

3.2 Paliperidone three month (PP3M) LAI has not previously been considered by the PBAC.

3.3 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. Paliperidone 3, 6 and 9 mg tablets were listed on 1 April 2008.

3.4 At its November 2010 meeting, the PBAC recommended the listing of paliperidone one month (PP1M) LAI on a cost minimisation basis compared with risperidone modified release injection.

3.5 Four atypical LAI antipsychotics are currently listed on the PBS for the treatment of schizophrenia. Risperidone fortnightly LAI was recommended for listing on a cost-effectiveness basis versus risperidone tablets in July 2004. Olanzapine one month LAI was recommended for listing in July 2009, based on clinical comparisons with risperidone LAI and olanzapine tablets, and priced versus olanzapine tablets. PP1M LAI (PP1M) was recommended for listing in November 2010 on a cost-minimisation basis versus risperidone LAI. Aripiprazole one month LAI was recommended for listing cost-minimisation basis compared to paliperidone LAI in July 2014.

For more detail on PBAC's view, see section 7 "PBAC outcome".

4 Clinical place for the proposed therapy

4.1 Schizophrenia is a severe, chronic, relapsing psychiatric illness characterised by disturbances in speech, perception, cognition, volition and emotion.

4.2 The submission proposed that PP3M LAI would be used as maintenance treatment for patients who have been stable on PP1M LAI for at least four months. PP3M LAI

would provide an alternate LAI treatment with a less frequent dosing schedule to those already listed on the PBS.

For more detail on PBAC's view, see section 7 "PBAC outcome".

5 Comparator

5.1 PP1M LAI. This was considered the appropriate comparator.

5.2 If listed, PP3M LAI would be the first long acting antipsychotic with a duration of action greater than four weeks. The ESC considered that clinicians/patients may preferentially commence on PP1M LAI over other LAI options, and further that patients may switch from another injectable to PP1M LAI, in order to access the option of PP3M LAI.

For more detail on PBAC's view, see section 7 "PBAC outcome".

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (5) via the Consumer Comments facility on the PBS website. The comments described that a reduction in dosing frequency would result in greater adherence to therapy, particularly in non-compliant patients, which would result in reduced risk of relapse and hospitalisation.

Clinical trials

6.3 The submission was based on one head-to-head trial comparing PP3M LAI to PP1M LAI as maintenance treatment for schizophrenia in patients who had been stabilised on PP1M LAI for four months prior to randomisation.

6.4 Details of the trial presented in the submission are provided in table 1 below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
R092670-PSY-3011	A randomized, multicentre, double-blind, non-inferiority study of paliperidone palmitate 3 month and 1 month formulations for the treatment of patients with schizophrenia. Savitz AJ, Xu H, Gopal S, et al. Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomised, multicentre, double-blind, non-inferiority study.	10 June 2015 International Journal of Neuropsychopharmacology 2016; 19(7):1-14

6.5 The key features of the direct randomised trial are summarised in table 2 below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Paliperidone three month LAI vs. paliperidone one month LAI					
PSY-3011	1016	MC, R, DB, PG 17 weeks open label phase 48 weeks double blind phase	Low	Patients with schizophrenia on a stable dose of paliperidone one month LAI	Relapse, PANSS

Source: compiled during the evaluation

Abbreviations: LAI, long acting injectable; DB, double blind; MC, multi-centre; R, randomised; PG, parallel group; PANSS, positive and negative syndrome scale for schizophrenia.

Comparative effectiveness

6.6 Table 3 summarises the results of the primary outcome (proportion of patients relapse free at 48 weeks) from Trial PSY-3011.

Table 3: Difference in percentage of relapse free patients in the double blind phase of Trial PSY-3011

Outcome	Paliperidone three month LAI	Paliperidone one month LAI	Risk Difference % (95% CI)
Proportion of patients who were relapse free, including patients who withdrew, n/N (%)			
Per protocol analysis	421/458 (91.2)	445/490 (90.0)	1.2 (-2.7, 5.1)
mITT analysis			
Proportion of patients who were relapse free, excluding patients who withdrew, n/N (%)			
Safety analysis set			
mITT analysis			

Source: Table B.6-1, p.48 of the submission; Table 34, p. 98 (PP analysis), Table 35, p. 100 (mITT analysis), Table 12, p.71 (safety analysis set) and Table 13, p.72 (mITT analysis) of the clinical trial report. Results presented in italics calculated during the evaluation

Abbreviations: CI, confidence interval; mITT, modified intention to treat

6.7 The proportion of patients remaining relapse-free over the 48 week double blind phase was not statistically significantly different between treatments in any of the analysis sets presented. PP3M LAI demonstrated non-inferiority to PP1M LAI with the lower bound of the 95% confidence interval within the pre-specified non-inferiority margin of -15%.

6.8 Results for secondary efficacy outcomes, including the change in the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), Clinical Global Impression-Severity (CGI-S) and Personal and Social Performance (PSP) scores, showed no statistically significant difference between PP3M LAI and PP1M LAI.

Comparative harms

6.9 The incidence of treatment related adverse events and serious adverse events were similar across both PP3M LAI and PP1M LAI treatment groups.

6.10 The most common adverse events were increased weight, nasopharyngitis, anxiety, headache and injection site pain/induration.

- 6.11 The incidence of extrapyramidal symptoms (EPS) or EPS-related events, and the use of medications for the treatment of EPS, were similar across treatment groups. Akathisia was the most common EPS event.
- 6.12 PP3M LAI has a safety profile that appears to be similar to that of PP1M LAI. However, as a relatively new formulation which is currently only approved for marketing in the US (FDA, May 2015), its full adverse effect profile will only be established after more widespread and long term use in a broader patient population.
- 6.13 The ESC considered that PP3M and PP1M were likely to have comparable safety profiles, but noted some differences in the PSY-3011 trial results, such as a different distribution of QTc prolongation between treatment groups, which found a QTc of >30-60 seconds in 58/494 patients in the PP3M group and 29/494 patients in the PP1M group. The ESC also considered it was outside the normal function of a General Practitioner to monitor for QTc prolongation in schizophrenia patients.
- 6.14 The ESC noted other potential concerns raised by the ACPM, including the inability to rapidly discontinue treatment in response to an adverse event and concerns relating to the use of PP3M in women of childbearing age if an unplanned pregnancy were to occur while being treated with PP3M. The concerns raised by the TGA Delegate and echoed in the Commentary and by the ESC were addressed by Janssen (in consultation with the TGA Delegate) by including additional statements regarding these issues in the precautions section of the Product Information. These changes were made following the ACPM meeting and subsequent to Janssen's PSCR.

Clinical claim

- 6.15 The submission described PP3M LAI as non-inferior in terms of comparative efficacy and equivalent in terms of comparative safety compared to PP1M LAI. This claim was adequately supported for both efficacy and safety for the maintenance treatment of schizophrenia and considered reasonable by the ESC.
- 6.16 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.17 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.18 The equi-effective doses were directly informed by the dose conversion used in Trial PSY-3011. The submission claimed the PP3M LAI dose is equivalent to 3.5 times the stable dose of PP1M LAI. The equi-effective doses are presented in Table 4. The equi-effective doses based on the clinical trial data were reasonable.

Table 4: Equi-effective doses of paliperidone one month LAI and three month LAI for the maintenance treatment of patients with schizophrenia.

Paliperidone three month dose (mg)	Paliperidone one month equi-effective dose (mg)
175	50
263	75
350	100
525	150

Source: Table D.1-1, p.68 of the submission.

- 6.19 The proposed price in the submission for PP3M LAI was based on the equi-effective doses of PP1M LAI, and included drug costs and a cost offset for reduced administration costs (MBS Level B GP consultation). This approach resulted in a higher price for PP3M LAI compared to PP1M LAI.
- 6.20 The cost minimisation analysis presented in the submission used the dispensed price for maximum quantity (DPMQ) less weighted average patient co-payment. This was not appropriate. The cost minimisation analysis was revised during the evaluation based on the approved ex-manufacturer price (AEMP) (table 5).

Table 5: Cost minimisation using ex-manufacturer pricing

	Paliperidone one month	Paliperidone three months
Paliperidone one month 50mg versus paliperidone three months 175mg		
Drug therapy costs		
Prescriptions per 48 week period	12	4
AEMP per prescription	\$230.06	\$ [REDACTED]
Total cost of drug therapy over 48 weeks	\$2760.74	\$ [REDACTED]
Net difference in drug costs	\$ [REDACTED]	
Dose administration costs		
Dose administrations per 48 week period	12	4
GP standard consult (\$37.05 per visit; MBS item 23)	\$444.60	\$148.20
Total cost of treatment over 48 weeks	\$3205.34	\$3205.34
Net difference in treatment costs (paliperidone three month LAI – paliperidone one month LAI)	\$0.00	
Paliperidone one month 75mg versus paliperidone three months 263mg		
Drug therapy costs		
Prescriptions per 48 week period	12	4
AEMP per prescription	\$299.28	\$ [REDACTED]
Total cost of drug therapy over 48 weeks	\$3591.38	\$ [REDACTED]
Net difference in drug costs	\$ [REDACTED]	
Dose administration costs		
Dose administrations per 48 week period	12	4
GP standard consult (\$37.05 per visit; MBS item 23)	\$444.60	\$148.20
Total cost of treatment over 48 weeks	\$4035.98	\$4035.98
Net difference in treatment costs (paliperidone three month LAI – paliperidone one month LAI)	\$0.00	
Paliperidone one month 100/150mg versus paliperidone three months 350/525mg		
Drug therapy costs		
Prescriptions per 48 week period	12	4
AEMP per prescription	\$367.80	\$ [REDACTED]
Total cost of drug therapy over 48 weeks	\$4413.60	\$ [REDACTED]
Net difference in drug costs	\$ [REDACTED]	
Dose administration costs		

	Paliperidone one month	Paliperidone three months
Dose administrations per 48 week period	12	4
GP standard consult (\$37.05 per visit; MBS item 23)	\$444.60	\$148.20
Total cost of treatment over 48 weeks	\$4858.20	\$4858.20
Net difference in treatment costs (paliperidone three month LAI – paliperidone one month LAI)	\$0.00	

Source: Compiled during the evaluation

Abbreviations: AEMP, approved ex-manufacturer price; LAI, long acting injectable; MBS, Medicare Benefits Schedule

- 6.21 During the evaluation it was noted that savings to the MBS associated with a reduction in medical visits are unlikely to be realised in practice as the purpose of these visits may not be specific to paliperidone administration.
- 6.22 The Pre-Sub-Committee Response (PSCR, p3) argued the approach taken in the submission was consistent with that for PP1M, in which reduced GP visits were accepted against the comparator of risperidone LAI, which is administered fortnightly.
- 6.23 The ESC noted that the cost offsets for reduced GP visits used in the cost minimisation analysis resulted in a price premium for PP3M over equivalent doses of PP1M.
- 6.24 The ESC also noted the advice of the ACPM, which ‘emphasised that contact between patient and health practitioner should be based on clinical need and not be based solely on the administration interval for medicines’. Further, the ESC considered that reasons for GP visits may include proper clinical management of schizophrenia, such as monitoring of glycated haemoglobin (HbA1c) and lipid levels while being treated with paliperidone. On that basis, the ESC agreed it was unlikely that the reduction in GP visits proposed in the submission would be fully realised in practice.
- 6.25 In the Pre-PBAC response the request for a cost offset for reduced GP consultations associated with less frequent administration of PP3M was withdrawn.
- 6.26 The submission requested a flat pricing structure for the 350mg and 525mg strengths of PP3M LAI, consistent with pricing for the highest doses of PP1M LAI (paliperidone PSD, November 2010).

Drug cost/patient /year:

- 6.27 The revised drug cost per patient per year taking into account the prices in the Pre-PBAC response were estimated to be:
- \$ [REDACTED] for PP3M LAI 175mg (DPMQ \$ [REDACTED]; 4.35 injections per year [52.14 weeks per year/12 weeks])
 - \$ [REDACTED] for PP3M LAI 263mg (DPMQ \$ [REDACTED]; 4.35 injections per year [52.14 weeks per year/12 weeks])
 - \$ [REDACTED] for PP3M LAI 350mg/525mg (DPMQ \$ [REDACTED]; 4.35 injections per year [52.14 weeks per year/12 weeks]).
- 6.28 The drug costs per patient per year for PP1M LAI were estimated to be:

- \$ [REDACTED] for PP1M LAI 50mg (DPMQ \$ [REDACTED]; 13.04 injections per year [52.14 weeks per year/4 weeks])
- \$ [REDACTED] for PP1M LAI 75mg (DPMQ \$ [REDACTED]; 13.04 injections per year [52.14 weeks per year/4 weeks])
- \$ [REDACTED] for PP1M LAI 100/150mg. (DPMQ \$ [REDACTED]; 13.04 injections per year [52.14 weeks per year/4 weeks]).

Estimated PBS usage & financial implications

6.29 This submission was not considered by DUSC. The submission presented a market share approach, with estimates based on extrapolated trends of use of PP1M LAI derived from Department of Human Services (DHS) prescription data for the five years to April 2016. The submission assumed PP3M LAI would only substitute for a proportion of the PP1M LAI market. The financial estimates below are from the submission and hence do not include the reduced prices proposed in the Pre-PBAC response for PP3M LAI. The redacted table below shows that at Year 5 the estimated number of prescriptions was over 200,000 per year and the net cost to the PBS would be less than \$10 million per year.

Table 6: Estimated utilisation and cost to the PBS in the first five years of listing of paliperidone three months

	Year 1	Year 2	Year 3	Year 4	Year 5
Paliperidone three months not listed					
Total prescriptions	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to the PBS/RPBS (DPMQ)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total patient co-payments ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to the PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Paliperidone three months listed					
Market share (% of paliperidone one month LAI market)	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%
Total prescriptions	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Paliperidone one month	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Paliperidone three months	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Total PBS/RPBS prescriptions	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to the PBS/RPBS (DPMQ)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Paliperidone one month	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
- Paliperidone three months	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
- Total cost to the PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total patient co-payments	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Paliperidone one month	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
- Paliperidone three months	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
- Total co-payments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to the PBS/RPBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Paliperidone one month	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
- Paliperidone three months	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
- Net cost PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Difference in costs to the PBS (paliperidone three months listed – paliperidone three months not listed)					
Costs to the PBS/RPBS at DPMQ	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patient co-payments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: compiled during the evaluation using 'Invega Trinza financial implications' spreadsheet provided with the submission
Abbreviations:

^a Weighted average patient co-payment calculated in the commentary used to determine estimate of total patient co-payments

- 6.30 The Pre-PBAC response included an updated estimate of net financial cost to government based on the proposed prices in the Pre-PBAC response (table 7). The redacted table below shows that the net cost to the PBS would be less than \$10 million per year. The PBAC noted that these estimates had not been verified.

Table 7: Updated net financial implications to the Government health budgets

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to the MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net financial implications	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Scheme.

- 6.31 The additional PBS/RPBS cost for PP3M LAI in table 6 is due to the inclusion of a cost offset for savings to the MBS resulting from reduced cost of administration for the three month compared to the one month LAI. The submission claimed the overall cost to government will be neutral, with additional costs to the PBS offset by an equivalent saving to the MBS as a result of less frequent drug administrations. The PBAC noted a slight cost to Government in the revised financial estimates in the Pre-PBAC response.
- 6.32 The submission’s original estimates of the costs to Government health budgets may be underestimated because:
- Estimated savings derived from avoided GP visits may not be realised in clinical practice. The PBAC noted that this was removed from the proposal in the Pre-PBAC response.
 - No allowance was made for patients switching from other oral or injectable antipsychotics to PP3M LAI via PP1M LAI (if prescribers feel their patient would be better managed using a three month LAI). Therefore, the availability of PP3M LAI may grow the paliperidone LAI market.
- 6.33 The PSCR (p1-3) argued that clinical guidelines do not support switching from oral to injectable antipsychotics unless clinically indicated, and patients’ aversion to injections is common. Further, the PSCR argued that dosing frequency is not a significant driver of LAI choice as risperidone retains a substantial market share amongst the injectables and that the efficacy and safety profiles of treatments are the key consideration of treatment choice..
- 6.34 The ESC considered that clinicians/patients may preferentially commence on PP1M LAI over other LAI options. Alternatively, clinicians/patients may switch from another injectable to PP1M LAI, in order to access the option of PP3M LAI. Both could potentially increase the number of PP1M LAI prescriptions, then PP3M LAI prescriptions, for the financial estimates.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority required (STREAMLINED) listing of paliperidone 3-month injection for schizophrenia, on a cost minimisation basis with equivalent doses of paliperidone once monthly injection.
- 7.2 The PBAC considered the equi-effective doses to be:
- One injection of PP3M 175 mg = three injections of 50 mg PP1M
 - One injection of PP3M 263 mg = three injections of 75 mg PP1M
 - One injection of PP3M 350 mg = three injections of 100 mg PP1M
 - One injection of PP3M 525 mg = three injections of 150 mg PP1M
- 7.3 The PBAC considered the clinical claim that PP3M was non-inferior in terms of comparative efficacy and equivalent in terms of comparative safety compared to PP1M to be reasonable.
- 7.4 The PBAC approved the proposed restrictions, including the addition of wording proposed by the PBAC Secretariat that patients must be stabilised on PBS-subsidised paliperidone once-monthly injection for at least 4 consecutive months.
- 7.5 The PBAC considered there was a clinical place for PP3M, as it would provide an extended duration LAI treatment with less frequent dosing compared with other PBS listed therapies and may contribute to improvements in patient comfort, carer burden and access for patients in rural and remote areas.
- 7.6 The PBAC considered that PP1M was the appropriate comparator, but noted that long acting injectable forms of risperidone, aripiprazole and olanzapine were also listed on the PBS at comparable prices for a course of treatment, taking into account the different injection frequencies.
- 7.7 The PBAC considered the single randomised head to head clinical trial (PSY-3011) was of good quality and the population was generalisable to the Australian patient population.
- 7.8 The PBAC considered that PP3M demonstrated non-inferiority to PP1M at the proposed equi-effective doses with the lower bound of the 95% confidence interval within the pre-specified non-inferiority margin of -15%. The PBAC noted there was no statistically significant difference between PP3M and PP1M with regards to secondary efficacy outcomes including change in PANSS, CGI-S and PSP scores.
- 7.9 The PBAC considered that the safety profile of PP3M was similar to PP1M, and noted the incidence of treatment related adverse events and serious adverse events were similar across both PP3M and PP1M treatment groups. The PBAC noted that the ESC raised concerns about differences in QTc prolongation between the treatments, and the arguments in the Pre-PBAC response that QTc prolongation is thought to occur quickly after oral dosing, and would therefore likely be detected during tolerability testing.
- 7.10 The PBAC noted the sponsor withdrew its request for a cost offset for reduced GP

visits with PP3M in the Pre-PBAC response, and proposed that PP3M be cost minimised against PP1M on the basis of drug costs only.

- 7.11 The PBAC considered there was some uncertainty with the utilisation and financial estimates, and agreed with the ESC advice that it was possible that patients may switch to PP3M via PP1M, from other drugs for this indication, and therefore grow both the PP3M and PP1M markets, but was uncertain as to what extent this may occur.
- 7.12 The PBAC recommended that PP3M should not be treated as interchangeable with any other drugs as it is the first long acting injectable antipsychotic with a duration of action greater than one month.
- 7.13 The PBAC advised that PP3M is suitable for prescribing by nurse practitioners under a shared care model, where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan.
- 7.14 The PBAC recommended that the Early Supply Rule should not apply, as it does not apply to other LAI forms of paliperidone, risperidone or aripiprazole.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new items:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
PALIPERIDONE				
Aqueous solution for injection, 273mg, prefilled syringe	1	1		
Aqueous solution for injection, 410mg, prefilled syringe	1	1	Invega® Trinza™	Janssen-Cilag Pty Ltd.
Aqueous solution for injection, 546mg, prefilled syringe	1	1		
Aqueous solution for injection, 819mg, prefilled syringe	1	1		
Category / Program	GENERAL – General Schedule (Code GE)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Condition:	Schizophrenia			
PBS Indication:	Schizophrenia			
Restriction Level	/ <input type="checkbox"/> Restricted benefit			

Method:	<input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received and be stabilised on PBS-subsidised paliperidone once-monthly injection for at least 4 consecutive months.
Prescriber Instructions	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.
Administrative Advice	Patient dosage is to be determined as per the dose transition table in the Product Information based on the maintenance dose of paliperidone once-monthly injection. No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised.

9 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.

10 Sponsor's Comment

The sponsor had no comment.