



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

Name of medicine (INN):	<ul style="list-style-type: none">• Paliperidone 3mg, 6mg, 9 mg extended release tablet• Paliperidone (as palmitate) 50mg/0.50mL, 75mg/0.75mL, 100mg/mL, 150mg/1.5mL, prolonged- release suspension for injection (IM), pre-filled syringe
Indication:	For recurrence prevention and maintenance therapy for schizophrenia; for the treatment of acute manic episodes associated with bipolar I disorder ; for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants.
Date of deliberation:	01 July 2015 26 November 2015
Recommendation:	DISAPPROVAL
Clinical evidence:	<p>The Council noted in the ERG evaluation that a Cochrane meta-analysis showed that there is no significant difference in the mean Positive and Negative Syndrome Scale (PANSS) score between paliperidone and the currently listed risperidone, whether in tablet or injectable preparation. Same is true when paliperidone was compared with olanzapine and quetiapine.</p> <p>In terms of overall side effects (SEs), results showed that lesser SEs were observed among patients receiving paliperidone, however, there was no statistically significant difference in this observation. Likewise, paliperidone was also noted to have an advantage over risperidone only in terms of the occurrence of anticholinergic events.</p> <p><i>(See Attachment for the full ERG evaluation)</i></p>
Cost data:	Based on the cost data submitted by the proponent, there is a high price disparity between paliperidone and other antipsychotic agents. Paliperidone is more expensive at a monthly cost of Php 10,191 per box of 150 mg injection compared to olanzapine which has a drug price reference index (DPRI) of only Php 73.50 per 10 mg tablet (Php 2,205 per month). Likewise, the oral form of paliperidone is still twice as expensive as the other antipsychotic agents, i.e., 3mg & 6mg- Php 270, 9mg- Php 460.

(See Attachment).

Remarks:

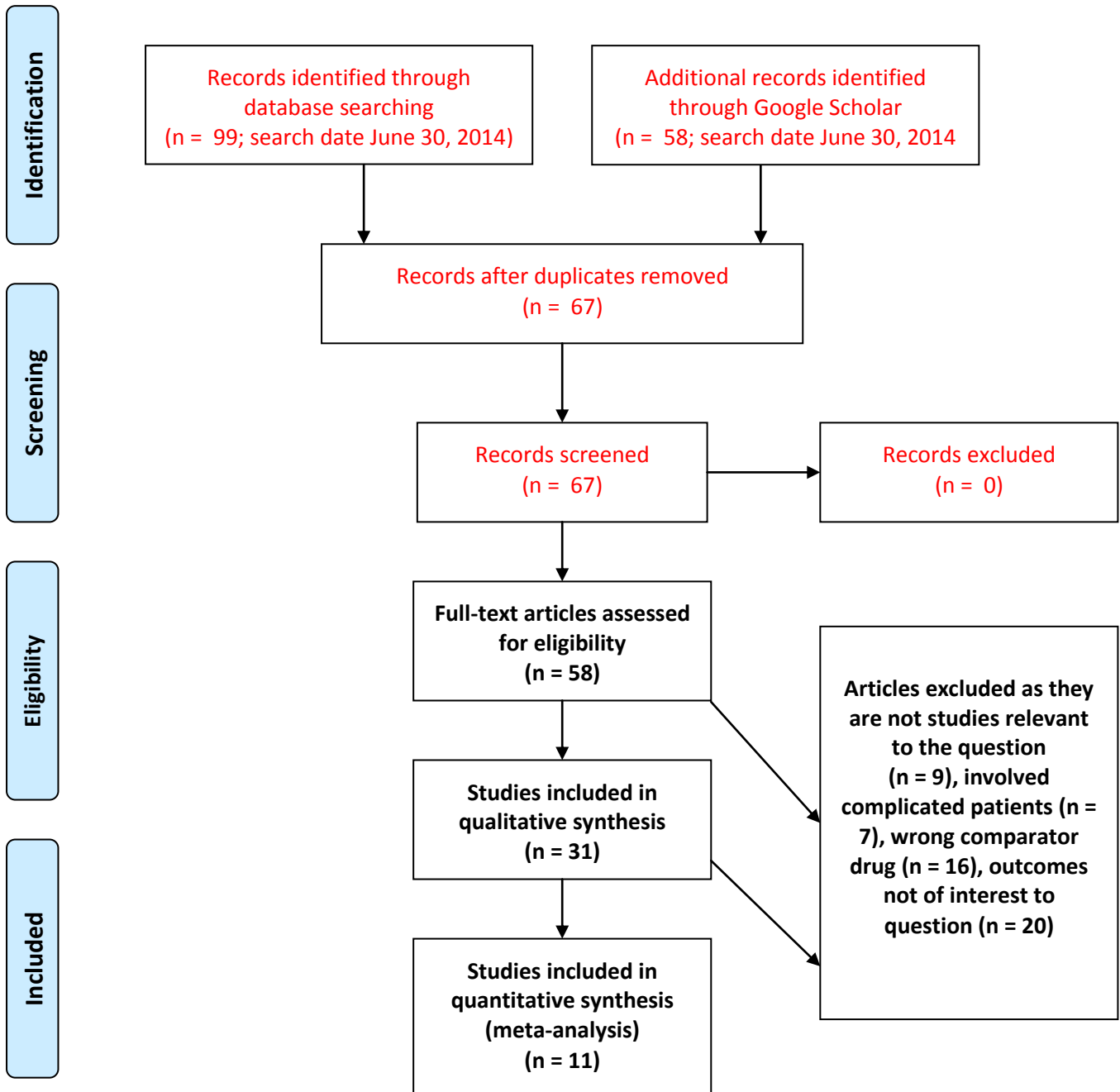
The ERG evaluated the documents submitted by the proponent to support their appeal and it was noted that most of the articles were uncontrolled studies or studies that involved economic modelling based on assumptions in foreign (not Philippine) health care systems. Thus, the ERG still maintains its findings in the review.

The Council concurred to this and given that the product has prohibitive cost and the proponent did not give a lower price offer, the initial recommendation to disapprove its inclusion still remains.

The Secretary of Health has officially disapproved the proposal to include paliperidone in the PNF.

PRISMA Table

PubMed search strategy was MESH search of “paliperidone” limited to randomized controlled trials and studies on human subjects. The yield was 99 articles. Additional records were reviewed from the search conducted by the other reviewer was 58.



What is the comparative efficacy and safety profile of paliperidone vs. all other antipsychotic medicines in the treatment of schizophrenia and/or bipolar I disorder and schizoaffective disorders?

- Specifically compared to similar preparation i.e. long acting injectables.

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS	Paliperidone		Comparator drug			
					(including adverse events)	No. of events *	Total # of patients	No. of events *	Total # of patients		
1	McEvoy et al. JAMA. 2014	RCT	311 adults with schizophrenia or schizoaffective disorder	Paliperidone palmitate vs. haloperidol decanoate	Efficacy failure	49 (33.8%)		47 (32.4%)			
					Weight gain	2.17 kg	95% CI 1.25 & 3.09	-0.96 kg	95% CI -1.88 & -0.04		
					Akathisia rating as side effect	0.45	95% CI 0.31 & 0.59	0.73	95% CI 0.59 & 0.87		
2	Fu, et al, 2014	post-hoc analysis	recently diagnosed schizophrenia (≤ 5 years)	Paliperidone palmitate vs. risperidone	Any adverse events	54.7%	161	50.3%	173		
3	Hu et al. Psychopharmacol. 2013	RCT	80 patients with schizophrenia	Paliperidone vs. olanzapine	Change in PANSS score	-20.33	95% CI -17.66 and -23.01	-23.39	95% CI -20.34 and 26.45		
					Weight gain	2.68		4.66			
					Adverse event	7.5%		20.0%			
4	Li et al. Neuropsychopharmacol Biol Psychiatry. 2011	RCT	452 schizophrenia patients	Paliperidone injection vs. risperidone injection	Change in Clinical Global Impression-Severity scale (CGIS)	- 1.5 (SD 1.24)	229	- 1.7 (SD 1.16)	223		
					Personal and Social Performance Scale	16.8 (SD 14.76)		18.6 (SD 13.92)			
					Adverse event	73%		75%			
5	Pandina et al. Prog Neuropsychoph	RCT	1,220 schizophrenia patients	Paliperidone injection vs. risperidone	Change in Positive and Negative Symptoms Scale	- 18.16 (SD 15.45)		- 17.9 (SD 14.24)			

	armacol Biol Psychiatry. 2011			injection	(PANSS) Overall adverse event	57.9%		52.8%			
6	Gopal et al. Int J Psychopharmacol 2010	RCT	109 schizophrenia patients	Paliperidone vs. quetiapine	Change in QT interval Any side effect	1.1 (SD1.78) 36	39 44	6.1 (SD 1.78) 41	37 43		
7	Canuso et al. Am J Psychiatry	RCT	399 acute schizophrenia patients	Paliperidone ER vs. quetiapine (2 arms of 3 arm study)	Change in PANSS Adverse event leading to discontinuation	-23.4 6.3%		-17.1 10.1%			
8	Kramer et al. Int J Neuropsychopharmacol. 2010	RCT	197 schizophrenia patients	Paliperidone vs. placebo	Change in PANSS Treatment-emergent adverse event EPS side effect	- 7.8 2% 8%	(SD 19.4)	6.2 10% 1%	(SD 18.3)		
9	Nussbaum and Stroup. Cochrane. 2012	Meta-analysis	2 RCTs with 1,969 schizophrenia patients	Paliperidone vs. risperidone	Recurrence of psychotic symptoms	1.23 (95% CI 0.98 and 1.53)					

*group means with standard deviations may be reported if the data are continuous

EVIDENCE TABLE 2: GRADE EVIDENCE PROFILE TABLE

QUALITY ASSESSMENT							SUMMARY OF FINDINGS				Importance	
							No. of patients		Effect			Over-all Quality
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute MD		
Outcome: Recurrence of symptoms												
1	Meta-analyses	No	No	No	No				1.23 (95% CI 0.98 and 1.53)		High	Critical

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

<p align="center">PARAMETER (Indicate information for intended recipient)* <i><u>INTENDED RECIPIENT:</u></i></p>	<p align="center">NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</p>	<p align="center">CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</p>	<p align="center">REFERENCES</p>
<p>COST PER DOSAGE UNIT (in PhP)</p> <p>a. Proposed list price to the government</p> <p>b. Current prevailing market price</p>	<p>Paliperidone¹ prolonged release suspension for inj Php 10,191 (same price for 50mg/0.5mL, 75mg/0.75mL, 100mg/mL, 150mg/1.50mL)</p> <p>Paliperidone¹ tab 3mg & 6mg- Php 270 9mg- Php 460</p>	<p>Olanzapine² Php 73.50 per 10 mg tablet</p> <p>Risperidone² Php 3,398.50 per 25 mg vial Php 11.55 per 2 mg tablet Php 8 per 4 mg tablet</p>	<p>¹company submission ²DPRI</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>Parenteral¹: Day 1- 150 mg One week later- 100 mg Monthly maintenance dose- 75 mg</p>	<p>30 tablets a month at 10 mg daily recommended maintenance dose</p> <p>Risperidone: 4-6 mg per day Oral risperidone should be given 3 weeks following the first injection</p>	<p>¹company submission</p> <p>www.drugs.com</p>
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>Php 30,573for injection (for 2 months)</p> <p>Php 8,100 to 13,800 for tablet (per month)</p>	<p>Olanzapine: Php 2,205 per month</p> <p>Risperidone: Php 3,694.50 (for 2 months)</p>	
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (PhP)</p>	<p align="center">None</p>	<p align="center">None</p>	
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p>Php 30,573for injection</p> <p>Php 8,100 to 13,800 for tablet</p>	<p>Php 2,205 per month</p>	
<p>ESTIMATED NUMBER OF PATIENTS WITH THE</p>	<p>0.3 % of adult population or 21 million</p>	<p>0.3 % of adult population or 21 million worldwide</p>	<p align="center">WHO http://www.who.int/</p>

DISEASE/CONDITION WHO WILL USE THE MEDICINE	worldwide		mental_health/management/schizophrenia/en/
QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)			
DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)			

REVIEWERS' RECOMMENDATIONS

Literature Search

- A total of 11 studies among patients with schizophrenia were included in this review. There were 7 RCTs and 1 meta-analysis or pooled analysis of multiple RCTs. There were 2 health economic analyses.

Effectiveness

- We included a review of one RCT that compared paliperidone with placebo that showed paliperidone to be an effective anti-psychotic medication.
- The pooled analysis 3 RCTs showed a slightly better effectiveness of paliperidone compared to other anti-psychotics in terms of PANSS score but the difference was not statistically significant. One of the studies however showed advantage of paliperidone over quetiapine.
- In terms of overall side effects, there is lesser side effect noted among the patients receiving paliperidone. However, a meta-analysis showed that paliperidone had a higher recurrence rate over other anti-psychotic but was not statistically significant. In addition, there is a higher weight gain as a result of paliperidone treatment.
- In terms weighing for the risk benefit, our analysis shows that paliperidone does not offer any significant advantage over other anti-psychotic drugs.
- The 2 health economic analysis pointed out paliperidone is more cost-effective over olanzapine and with lower cost of treatment compared to other anti-psychotics. But this is from the European setting and perspective. In the local perspective, paliperidone has a higher cost compared to other anti-psychotic already listed in the PNDF.

Overall Recommendation

- Based on our findings, there is not enough evidence to recommend paliperidone to be included in the PNDF.

References

1. McEvoy JP(1), Byerly M(2), Hamer RM(3), Dominik R(3), Swartz MS(4), Rosenheck RA(5), Ray N(3), Lambert J(6), Buckley PF(1), Wilkins TM(3), Stroup TS(7). Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. *JAMA*. 2014 May 21;311(19):1978-87. doi: 10.1001/jama.2014.4310.
2. Fu DJ, Bossie CA, Sliwa JK, Ma YW, Alphs L. 2014. Paliperidone palmitate versus oral risperidone and risperidone long-acting injection in patients with recently diagnosed schizophrenia: a tolerability and efficacy comparison. *Int Clin Psychopharmacol*. 2014 Jan;29(1):45-55. doi:10.1097/YIC.000000000000006.
3. Hu et al. A randomized, 12-week study of the effects of extended release paliperidone (paliperidone ER) and olanzapine on metabolic profile, weight, insulin resistance, and β -cell function in schizophrenic patients. *Psychopharmacology*. DOI 10.1007/s00213-013-3073-1
4. Li H(1), Rui Q, Ning X, Xu H, Gu N. A comparative study of paliperidone palmitate and risperidone long-acting injectable therapy in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011 Jun 1;35(4):1002-8. doi: 10.1016/j.pnpbp.2011.02.001. Epub 2011 Feb 18.
5. Pandina G(1), Lane R, Gopal S, Gassmann-Mayer C, Hough D, Remmerie B, Simpson G. A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011 Jan 15;35(1):218-26. doi: 10.1016/j.pnpbp.2010.11.008. Epub 2010 Nov 16.
6. Gopal S(1), Hough DW, Xu H, Lull JM, Gassmann-Mayer C, Remmerie BM, Eerdeken MH, Brown DW. Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. *Int Clin Psychopharmacol*. 2010 Sep;25(5):247-56. doi: 10.1097/YIC.0b013e32833948fa.
7. Kramer M(1), Litman R, Hough D, Lane R, Lim P, Liu Y, Eerdeken M. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. *Int J Neuropsychopharmacol*. 2010 Jun;13(5):635-47. doi: 10.1017/S1461145709990988. Epub 2009 Nov 27.

Response to appeal on the reviewers' recommendation on Paliperidone

We reviewed the articles submitted to support the appeal on paliperidone. We found out that most of the submitted articles to support the appeal were uncontrolled studies or studies that involved economic modelling based on assumptions in foreign (not Philippine) health care systems. Thus we maintain the original findings of the ERG.

Because cost is significant issue for PNF, it is recommended that the manufacturer decrease the cost of paliperidone comparable to current anti-psychotics for it to be reconsidered for inclusion in the PNF.