

## 7.02 LURASIDONE

**40mg & 80mg, film coated tablets;**

**Latuda<sup>®</sup>; Commercial Eyes P/L for Dainippon Sumitomo Pharma Ltd.**

### 1 Purpose of Application

- 1.1 The submission sought an Authority Required (STREAMLINED) listing for lurasidone 40mg and 80mg tablets for the treatment of schizophrenia. The first submission was considered at the March 2014 PBAC meeting and rejected on the basis that non-inferiority with the comparators was not established given the fundamental limitations of the trials presented (PBAC Minutes March 2014, paragraph 7.1).

### 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	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LURASIDONE				Latuda <sup>®</sup> Dainippon Sumitomo Pharma Ltd
Tablet, 40mg, 30	1	5		
Tablet, 80mg, 30	1	5		

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
Episodicity:	<del>Chronic</del>
Condition:	Schizophrenia
PBS Indication:	Schizophrenia
Treatment phase:	<del>Maintenance</del>
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<del>Not controlled satisfactorily, or are intolerant to atypical anti-schizophrenia agents such as olanzapine, quetiapine and risperidone;</del>  OR <del>In whom weight control and cardiometabolic issues are of concern</del>

- 2.2 The listing was requested on a cost minimisation basis compared to ziprasidone and aripiprazole (mixed comparator). The requested maximum quantities are not sufficient to supply patients prescribed 120mg daily. The PBAC noted that international utilization data showed that majority of lurasidone doses used are 40 mg or 80mg daily.
- 2.3 The requested restriction is narrower than that requested in the March 2014 submission, and limits the use of PBS subsidised lurasidone to those patients not controlled satisfactorily, or intolerant to, atypical antipsychotic agents such as olanzapine, quetiapine and risperidone (second line therapy), or in whom weight control and cardiometabolic issues are of concern (first line therapy). The requested listing is inconsistent with the PBS listing for 'other antipsychotic drugs, including the nominated comparators, which are listed for 'schizophrenia'. The ESC noted that it is unlikely to be feasible to implement a second line listing that will not 'leak' as an Authority Required (STREAMLINED) listing. The ESC also noted that the sponsor is willing to work with the Department of Health with respect to the restriction wording (Pre-Sub-Committee Response (PSCR), p1).

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

### 3 Background

3.1 Lurasidone was TGA registered on 16 April 2014 for adults with schizophrenia.

#### 3.2 Summary of the previous submission and current resubmission

	Lurasidone, March 2014	Current resubmission
Requested PBS listing	• Authority Required (STREAMLINED) - Schizophrenia.	• Authority Required (STREAMLINED) - Schizophrenia, in patients not controlled satisfactorily, or intolerant to atypical anti-schizophrenia agents such as olanzapine, quetiapine and risperidone, <i>OR</i> in whom weight control and cardiometabolic issues are of concern (first line therapy).
Requested price (DPMQ)	• Lurasidone 40mg tabs (90) \$ [REDACTED] (\$ [REDACTED]/mg AEMP). • Lurasidone 80mg tabs (60) \$ [REDACTED] (\$ [REDACTED]/mg AEMP). Corrected for price reductions during evaluation: • Lurasidone 40mg tabs (90) \$ [REDACTED] (\$ [REDACTED]/mg AEMP). • Lurasidone 80mg tabs (60) \$ [REDACTED] (\$ [REDACTED]/mg AEMP).	• Lurasidone 40mg tabs (30) \$ [REDACTED] (\$ [REDACTED]/mg AEMP). • Lurasidone 80mg tabs (30) \$ [REDACTED] (\$ [REDACTED]/mg AEMP).
Main comparator	• Main comparator ziprasidone, with secondary comparators olanzapine and quetiapine. <b>PBAC Comment:</b> Ziprasidone accepted as appropriate main comparator, but risperidone and paliperidone may also be appropriate secondary comparators (March 2014 Minutes, para.5.1-5.2).	• Main comparators ziprasidone and aripiprazole, given lurasidone is expected to be used as second line therapy or when other first line therapies are not appropriate.
Clinical evidence	• One 3 week safety and tolerability study (Trial 254) comparing high dose lurasidone and ziprasidone, two RCTs (Trials 231 and 233) providing direct head-to-head comparisons between lurasidone and olanzapine or quetiapine, with extension studies and one multi-treatment analysis (Leucht 2013) included during the evaluation. • Key outcomes: Change in PANSS, responder rates PANSS, time to relapse PANSS and change in CGI-S,	• Formal indirect comparison of lurasidone versus ziprasidone or aripiprazole, with olanzapine as the common comparator, using one trial for each comparison; lurasidone vs olanzapine (Trial 231), ziprasidone vs olanzapine (Breier 2005) and aripiprazole vs olanzapine (Kane

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	Lurasidone, March 2014	Current resubmission
	CDSS and MADRS.	2009). • Key outcomes; Change in PANSS total score and subscales and change in CGI-S.
Key effectiveness data	<ul style="list-style-type: none"> <li>• In Trial 254 the difference in mean change in PANSS between lurasidone and ziprasidone was -1.8 [-4.3, 0.7] but neither treatment reduced PANSS scores by the minimum clinically important difference (MCID) of 7 points.</li> <li>• In Trial 231 there was little difference in mean change in PANSS between lurasidone 40mg (-9.7 [-15.3, -4.1]) and 120mg (-7.5 [-13.4, -1.7]) or olanzapine 15mg (-12.6 [-18.2, -7.1]).</li> <li>• In Trial 233 there was little difference in mean change in PANSS between lurasidone 160mg/day (-16.2 [-21.2, -11.2]) and quetiapine 600mg/day (-17.5 [-22.5, -12.4]).</li> <li>• In the multi-treatment meta-analysis by Leucht et al 2013, olanzapine was statistically significantly more effective than lurasidone. No statistically significant difference was observed between lurasidone and quetiapine or lurasidone and ziprasidone, but the trend in both comparisons did not favour lurasidone.</li> </ul> <p><b>PBAC Comment:</b> Overall, the clinical data provided in the submission, or identified during the evaluation (Leucht et al) failed to establish non-inferiority of lurasidone with the main comparator ziprasidone.</p>	• See para 6.8 below.
Key safety data	<ul style="list-style-type: none"> <li>• More patients treated with lurasidone reported extrapyramidal side effects, such as akathisia, compared to olanzapine (17.3% vs 7.4%) and quetiapine (7.7% vs 1.7).</li> <li>• Fewer patients treated with lurasidone reported weight gain compared to olanzapine (1.7% vs 20.5%) or quetiapine (6.0% vs 8.2%).</li> </ul> <p><b>PBAC Comment:</b> The safety profile of lurasidone appeared to be similar to ziprasidone, but noted the effect of the short trial duration on the reliability of a safety conclusion.</p>	• See para 6.12 below.
Clinical claim	<ul style="list-style-type: none"> <li>• Equivalence in terms of comparative effectiveness and safety to ziprasidone, olanzapine and quetiapine.</li> </ul> <p><b>PBAC Comment:</b> Claims of equivalence were not adequately supported as the comparison with ziprasidone was based on one short trial of patients with stable chronic schizophrenia in which neither lurasidone nor the main comparator ziprasidone reduced the PANSS score by the MCID of 7 points. Non-inferiority with the secondary comparators but Trials 231 and 233 used olanzapine and quetiapine for assay sensitivity and between group efficacy analyses were not pre-specified (March 2014 Minutes, para 6.23-6.24).</p>	• Non-inferior effectiveness and similar safety to ziprasidone and aripiprazole (resubmission, p69).
Economic evaluation	<ul style="list-style-type: none"> <li>• Equi-effective doses based on clinical trials. lurasidone 120mg = 160mg ziprasidone (0.75:1) lurasidone 80mg = 15mg olanzapine (5.33:1) lurasidone 120mg = 630mg quetiapine (0.2:1)</li> <li>• Cost minimisation (trial based) versus a mixed comparator of ziprasidone, olanzapine and quetiapine. Sensitivity analysis including DDD based equi-effective doses.</li> </ul> <p><b>PBAC Comment:</b> The equi-effective doses of lurasidone versus ziprasidone or olanzapine derived from fixed dose</p>	<ul style="list-style-type: none"> <li>• Equi-effective doses based on clinical trials. lurasidone 80mg = 114.15mg ziprasidone (0.7:1). lurasidone 80mg = 17.37mg aripiprazole (4.61:1).</li> </ul>

	Lurasidone, March 2014	Current resubmission
	trial were not reliable. Similarly, the equi-effective doses of lurasidone and quetiapine were confounded by high initial dose regimens used prior to flexible dose titration (March 2014 Minutes, para 6.27-30).	
Number of patients	• █████ in Year 1 increasing to █████ in Year 5 (March 2014 Minutes, para 6.33).	• █████ in Year 1 increasing to █████ in Year 5 (resubmission, p105).
Estimated cost to PBS	<ul style="list-style-type: none"> <li>• Drug costs (excluding co-payment) \$ █████ in Year 1 increasing to \$ █████ in Year 5.</li> <li>• Net cost (excluding co-payment) \$ █████ in Year 1 increasing to \$ █████ in Year 5 (March 2014 Minutes, para 6.33).</li> </ul> <p><b>PBAC Comment:</b> The cost estimates were based on epidemiological data collected before 1995, and included unsupported assumptions about market uptake, unreasonable estimates of market share and were based on single selected dose strengths of lurasidone and comparators, and were therefore highly uncertain.</p>	<ul style="list-style-type: none"> <li>• Drug costs (excluding co-payment) \$ █████ in Year 1 increasing to \$ █████ in Year 5.</li> <li>• Net saving (excluding co-payment) \$ █████ in Year 1 increasing to \$ █████ in Year 5 (resubmission pp.104-107).</li> </ul>
PBAC decision	<ul style="list-style-type: none"> <li>• Rejected.</li> </ul> <p><b>PBAC Comment:</b> Non-inferiority with the comparators was not established because of the fundamental limitations of the trials presented and the cost-minimisation approach used was not justified.</p>	-

Source: Compiled during the evaluation

Abbreviations: CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression – Severity of illness; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Symptom Scale.

#### 4 Clinical place for the proposed therapy

- 4.1 The use of atypical antipsychotic medicines in schizophrenia is patient centred, aiming for maintenance of efficacy and patient compliance, minimal relapse episodes and tolerability of adverse events. Switching between agents is common, and often related to tolerability of adverse events such as weight gain and extrapyramidal side effects.
- 4.2 The resubmission proposed that lurasidone will be used when drugs such as olanzapine, quetiapine and risperidone are not effective or not tolerated, or when weight control and cardiometabolic issues are of concern, similar to the place in therapy of ziprasidone and aripiprazole. The resubmission argued that there is a clinical need for another PBS listed weight-neutral atypical antipsychotic medicine in the treatment of schizophrenia, in addition to ziprasidone and aripiprazole.

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

#### 5 Comparator

- 5.1 The submission nominated a mixed comparator of ziprasidone and aripiprazole. The evaluation noted that while ziprasidone is an appropriate comparator and belongs to the same pharmacological class as lurasidone (N05AE), aripiprazole belongs to a different pharmacological class and may not be an appropriate comparator (N05AX). The PSCR (p1) argued that a clinician's choice of suitable therapeutic agent would

not be driven by ATC class. The submission also did not identify distinct groups of patients with schizophrenia in whom one of the drugs ziprasidone or aripiprazole, but not the other, was appropriate.

- 5.2 Additionally, the evaluation noted that olanzapine, quetiapine, risperidone and paliperidone may also be appropriate secondary comparators, as noted by the PBAC during the consideration of the March 2014 lurasidone submission (PBAC Minutes, paragraph 5.1).
- 5.3 The ESC noted that if use is restricted to second line therapy, as proposed in the requested restriction, only clozapine would be an appropriate secondary comparator.

*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 that no consumer comments were received for this item.

### ***Clinical trials***

- 6.3 The resubmission was based on two formal indirect analyses comparing lurasidone (Trial 231) with ziprasidone (Kane 2009) and with aripiprazole (Breier 2005), with olanzapine as the common comparator. The multi-treatment meta-analysis by Leucht et al (2013), identified in the March 2014 commentary was presented as supportive evidence. Trial 254, a phase 2 three week safety trial comparing lurasidone with ziprasidone included in the previous submission, was appropriately excluded.

6.4 Trials and associated reports presented in the resubmission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>Lurasidone vs olanzapine</b>		
Trial 231 (Meltzer 2011)	Clinical Study Report: A phase 3 randomized, placebo and active comparator controlled clinical trial to study the safety and efficacy of two doses of lurasidone HCL in acutely psychotic patients with schizophrenia. Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study.	23 October 2009.  <i>American Journal of Psychiatry.</i> 2011; 168(9):957-967.
<b>Ziprasidone vs olanzapine</b>		
Breier 2005	Breier A, Berg PH, Thakore JH, et al. Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia.	<i>American Journal of Psychiatry.</i> 2005; 162(10):18799-1887.
<b>Aripiprazole vs olanzapine</b>		
Kane 2009	Kane JM, Osuntokun O, Kyrzhanovskaya LA, et al. A 28-week, randomized, double-blind study of olanzapine versus aripiprazole in the treatment of schizophrenia.	<i>Journal of Clinical Psychiatry.</i> 2009; 70(4):572-581.
<b>Atypical antipsychotic multi-treatment meta-analysis</b>		
Leucht (2013)	Leucht S, Cipriano A, Spenelli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis.	<i>The Lancet.</i> 2013; 382:951-962.

Source: Table B.3, pp.40-43 of the resubmission.

6.5 Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Comparison	Outcomes	Use in economic evaluation
<b>Lurasidone 40mg or 120mg (olanzapine 15mg common comparator)</b>							
Trial 231	478	R, DB, fixed dose 6 weeks	Low	Recent acute schizophrenia	Lurasidone vs olanzapine vs placebo	PANSS, CGI-S	Equi-effective doses
<b>Ziprasidone 80mg to 160mg (olanzapine 10mg to 20mg common comparator)</b>							
Breier 2005	548	R, DB, flex dose 28 weeks	Low	Recent acute schizophrenia	Ziprasidone vs olanzapine	PANSS, CGI-S, CGI-I	Equi-effective doses
<b>Aripiprazole 15mg to 30mg (olanzapine 10mg to 20mg common comparator)</b>							
Kane 2009	310	R, OL, flex dose 28 weeks	Low	Treatment naive	Aripiprazole vs olanzapine	PANSS, CGI-S, CGI-I	Equi-effective doses
<b>Atypical antipsychotic multiple treatment meta-analysis</b>							
Leucht 2013	43,049	212 randomised controlled trials reported between October 1955 and September 2012					NA

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.  
Source: compiled during the evaluation

6.6 The evaluation noted that trial 231 may not be applicable to the proposed PBS population (chronic maintenance therapy). The trial included only inpatients (acute management), was conducted over 6 weeks, used fixed dosing of 40mg or 120mg and did not include the requested lurasidone dose of 80mg daily. Further, patients with a wide range of metabolic and cardiac risk factors were excluded. The PBAC previously noted that Trial 231 included olanzapine for assay sensitivity and between group-efficacy analyses were not pre-specified (PSD, March 2014, p.7). The PSCR (p2) argued that the established efficacy of lurasidone is applicable to the PBS population, as Trial 231 was followed up by a long-term flexible dose extension study.

- 6.7 The evaluation considered that the trials may not be sufficiently comparable to be used in an indirect analysis. Trial 231 was conducted over 6 weeks in acute inpatients, while Breier (2005) and Kane (2009) included smaller proportions of inpatients (16%) compared to outpatients over 28 weeks (84%; i.e. primarily returning to maintenance management). Dosing in Trial 231 was fixed, versus flexible dosing in the ziprasidone and aripiprazole trials. The PSCR (p2) argued that there is sufficient homogeneity across the included trials in the indirect analysis. However, the ESC considered there remained concerns about exchangeability.

### Comparative effectiveness

- 6.8 Given the differences in the requested restriction and nominated comparators from the previous submission, and the unsuitability of the three week, phase 2 Trial 254 to the comparative analysis of lurasidone vs ziprasidone, results from the previous submission were not relevant to the resubmission

- 6.9 The table below presents the results from the indirect comparison provided with the resubmission.

Indirect comparison (olanzapine as common comparator) for difference in change from baseline to endpoint in mean PANSS total scores

Mean change PANSS total score	Lurasidone vs olanzapine 6 weeks	Ziprasidone vs olanzapine 28 weeks	Aripiprazole vs olanzapine 28 weeks	Indirect comparison Mean change (95% CI)	
				Lurasidone vs ziprasidone	Lurasidone vs aripiprazole
Lurasidone 40mg	3.00 (-2.41, 8.41)	<b>9.70 (5.03, 14.37)</b>	<b>4.60 (1.02, 8.18)</b>	-6.70 (-13.85, 0.45)	-1.20 (-7.99, 5.59)
Lurasidone 120mg	5.10 (-0.45, 10.65)			-4.60 (-11.86, 2.66)	<b>0.90 (-6.00, 7.80)</b>
Pooled*	4.05(-0.63, 8.73)			-5.65 (-12.27, 0.97)	-0.15 (-6.38, 6.08)

Source: Table 7, p.18 and Table 16, p.24 of the Indirect Treatment Comparison of Lurasidone Aripiprazole and Ziprasidone Report October 26 2014, attached to the resubmission.

Abbreviations: PANSS, Positive and Negative Symptom Scale; SD, standard deviation.

\* Methods used to pool results not provided. Note: statistically significant results in bold.

- 6.10 Olanzapine showed statistically significantly larger reductions in PANSS total score compared to ziprasidone (Breier 2005) and aripiprazole (Kane 2009). There was no statistically significant difference between lurasidone 40mg or 120mg strengths and olanzapine 15mg.
- 6.11 In the indirect analyses there was no statistically significant difference between lurasidone and its comparators, ziprasidone and aripiprazole, in change from baseline in PANSS total score. The upper bounds of the 95% confidence intervals were less than the MCID of 7 points, suggesting the claim that lurasidone is non-inferior to ziprasidone and aripiprazole may be reasonable. However, lurasidone 120mg failed to show non-inferiority vs aripiprazole at 8 weeks (0.50 95% CI [-6.10, 7.10]) and 28 weeks, the upper bound of the 95% confidence intervals exceeding the MCID of 7 points at both time points. The evaluation considered these results should be interpreted with caution, based on the concerns about applicability and exchangeability of the trials.
- 6.12 The resubmission acknowledged the lack of dose response between the lurasidone 40mg and 120mg treatment arms in Trial 231, but suggested this may be due to

small differences in severity of illness across treatment arms or a reflection of the variable nature of the disease and heterogeneity of clinical response in schizophrenia generally. However, the TGA Clinical Evaluation Report noted that there was no clear dose response for lurasidone, with only the 160mg/day dose providing significantly better efficacy compared to lower doses.

### **Comparative harms**

- 6.13 The most frequently reported adverse events in patients treated with lurasidone were headache (18-22%), nausea (8-11%), extra-pyramidal symptoms, akathisia (12-23%), somnolence (10-15%), agitation (6-12%), anxiety (10%), insomnia (12-13%) and dystonia (3-8%). This is consistent with the previous submission, the event rates from the long term extension studies and the lurasidone Product Information document.
- 6.14 The resubmission argued that lurasidone provides similar weight neutral and metabolic profile compared to ziprasidone and aripiprazole. This appears reasonable.

### **Clinical claim**

- 6.15 The resubmission described lurasidone as non-inferior in terms of comparative effectiveness and similar in terms of comparative safety over the main comparators ziprasidone and aripiprazole.
- 6.16 The indirect comparison showed the lurasidone 40mg and pooled doses (40mg and 80mg) are non-inferior to ziprasidone and aripiprazole, with the 95% CI within the MCID of 7 points on the PANSS total score. However, lurasidone 120mg did not show non-inferiority versus aripiprazole at 8 weeks or 28 weeks. The TGA Clinical Evaluation Report noted that there was no clear dose response in five short term trials of lurasidone, with only the 160mg/day dose providing significantly better efficacy compared to lower doses.

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

### **Economic analysis**

- 6.17 The submission presented a cost minimisation analysis against the mixed comparator of ziprasidone and aripiprazole.
- 6.18 The equi-effective doses were calculated relative to the common comparator olanzapine and estimated as:
- lurasidone 80mg = ziprasidone 114.15mg; and  
lurasidone 80mg = aripiprazole 17.37mg.
- 6.19 Similar to the previous submission, the equi-effective doses of lurasidone and olanzapine were based on the average of two fixed dose lurasidone treatment arms and a single fixed dose olanzapine arm in the 6 week Trial 231, but in the resubmission the average lurasidone dose was weighted by the number of patients in each arm. The PSCR (p3) noted that there is currently no gold standard method to derive dose equivalence between antipsychotics.

- 6.20 The evaluation noted that, during its consideration of the previous submission, the PBAC had noted that it was inappropriate to base the equi-effective doses of lurasidone and olanzapine on the average of two fixed dose regimens in Trial 231 when olanzapine showed numerically larger treatment effects in key outcomes (March 2014 Minutes, paragraph 6.29). Weighting of the lurasidone arms by numbers of patients randomised does not address this issue.
- 6.21 The PBAC noted that the cost-minimisation is sensitive to the equi-effective dose of lurasidone versus olanzapine, but considered that, on balance, the proposed equi-effective doses of lurasidone and ziprasidone were appropriate.
- 6.22 The proposed price of lurasidone is based on the equi-effective doses of aripiprazole and ziprasidone weighted by their respective PBS-volumes (■% and ■%, respectively).

Listed price of ziprasidone and aripiprazole with volume weighted price per mg

	Total services	Volume weight 2013-14	Therapeutic relativity vs lurasidone	AEMP/mg	Equi-effective AEMP/mg
Aripiprazole	172,215	■%	0.22:1	\$■	\$■
Ziprasidone	28,092	■%	1.42:1	\$■	\$■
Volume weighted equi-effective lurasidone AEMP/mg					\$■
Volume weighted equi-effective lurasidone AEMP/mg with 5% discount					\$■

- 6.23 With the proposed ■% discount compared to the weighted comparator, the lurasidone AEMP/mg is \$■. This compares with \$■/mg (corrected) for lurasidone 40mg and 80mg in the previous submission.
- 6.24 The ESC requested a comparison of the listings and prices of the PBS anti-psychotic medicines in order to compare the equi-effective doses and requested price of lurasidone to other therapies for schizophrenia. The ESC also noted that the pricing methodology used by the submission to calculate the ex-manufacturer price for lurasidone is unconventional and results in a price which is higher than that calculated using conventional methods.
- 6.25 The pre-PBAC response pointed out that the ESC advice had used an incorrect price for lurasidone in this comparison. This has been corrected in the table below.

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Price comparison of anti-psychotics

Drug	Lurasidone	Ziprasidone	Aripiprazole	Paliperidone	Olanzapine	Quetiapine	Risperidone	Clozapine
ATC Group	NO5AE	NO5AE	NO5AX	NO5AX	NO5AH	NO5AH	NO5AX	NO5AH
PBS Listing	Authority Required (STREAMLINED) – See Section 2	Authority Required (STREAMLINED) - Schizophrenia (1589)	Authority Required (STREAMLINED) - Schizophrenia (1589)	Authority Required (STREAMLINED) - Schizophrenia (4246)	Authority Required (STREAMLINED) - Schizophrenia (1589)	Authority Required (STREAMLINED) - Schizophrenia (1589)	Authority Required (STREAMLINED) - Schizophrenia (1589)	Authority Required (STREAMLINED) - Schizophrenia (4411)^
Formulary	F1	F2	F1	F1	F2	F2	F2	F2
Basis of recommendation	Seeking cost minimisation compared to ziprasidone and aripiprazole (mixed comparator).	Cost minimised to olanzapine.	Cost minimised to olanzapine.	Cost minimised to olanzapine.	Acceptable cost-effectiveness compared to risperidone.	Cost minimised to risperidone.		Listed 1993, pre-dates cost-effectiveness
Equi-effective dose per sub	80mg	114.15mg	17.37mg	N/A	15.032mg	N/A	N/A	N/A
Equi-effective dose per Therapeutic Relativity Sheets, (Table D1, 7.02 Comm.30*)	80mg	125.75mg	21.3mg	11.4 mg #	15.032mg	N/A	N/A	The usual effective daily dose is 200 mg to 600 mg (eTG)
Price (AEMP) for equi-effective dose for 30 days (based on submission presented equi-effective doses)	\$ [redacted] (submission method + [redacted] % discount**); \$ [redacted] (usual pricing method + [redacted] % discount**)	\$170.34	\$184.99	\$254.42	\$76.63	\$51.43 for 100 mg tds	\$27.40 for 2 mg bd	\$72.71 for 200mg d
Ex-man 1 Feb 2015	AEMP = \$ [redacted] per 80mg, 30	AEMP = \$179.07 per 60mg, 60	AEMP = \$212.99 per 20mg, 30	AEMP = \$187.49 per 9mg, 28	AEMP = \$71.52 per 15mg, 28	AEMP = \$51.43 for 100mg, 90	AEMP = \$27.40 for 2mg, 60	AEMP = \$242.38 for 200mg, 100

\* Assuming 80mg lurasidone: 15.032mg olanzapine as per Therapeutic Relativity Sheets – 1 December 2014.

# In the absence of dose equivalency for paliperidone being included in the submission, paliperidone dose calculated using paliperidone 9.83mg per day and olanzapine 12.91 mg per day, as per Therapeutic Relativity Sheets – 1 Dec 2014

\*\* The submission calculates a weighted per mg price for ziprasidone and aripiprazole based on current PBS usage of each strength of those drugs, and then calculates a lurasidone price weighted by their respective PBS-volumes ([redacted] % and [redacted] %, respectively). This gives a price of \$ [redacted] which is then discounted by [redacted] % to \$ [redacted]. The alternative, usual pricing method would be to use the ex-manufacture prices of ziprasidone 60 mg x 60 and aripiprazole 20 mg x 30 as the basis for calculating a lurasidone price (closest pack method). The alternative method results in an ex-man price of \$ [redacted], which if subject to a [redacted] % discount would be \$ [redacted]

^ where patient must be non-responsive to other neuroleptic agents; QR patient must be intolerant of other neuroleptic agents.

**Drug cost/patient/year: \$ [redacted] to \$ [redacted]**

6.26 \$ [redacted] to \$ [redacted] for lurasidone assuming doses of 40mg to 160mg/day. Compared to \$942.80 to \$6,854.21 for ziprasidone 40mg to 160mg/day and \$1,856.51 to \$3,696.60 for aripiprazole 10mg to 30mg/day.

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

**Estimated PBS usage & financial implications**

6.27 This resubmission was not considered by DUSC. Similar to the previous submission a mixed epidemiological/market share approach was used to estimate utilisation and financial implications to government.

**Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Pts from 1 <sup>st</sup> line ziprasidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pts from subseq. line ziprasidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pts from 1 <sup>st</sup> line aripiprazole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pts from subseq. line aripiprazole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients treated lurasidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number treated Mar 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts <sup>a</sup>	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts Mar 2014 <sup>b</sup>	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<b>Estimated cost to PBS (excl co-payment)</b>					
Drug cost to PBS <sup>c</sup>	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Drug cost to PBS Mar 2014 <sup>d</sup>	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net savings substitution	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net savings substitution Mar 2014	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>Estimated total net cost (excl co-payment)</b>					
Net cost PBS	-\$ [redacted]	-\$ [redacted]	-\$ [redacted]	-\$ [redacted]	-\$ [redacted]
Net cost PBS Mar 2014	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

Abbreviations: pts., patients; subseq., subsequent

Source: Compiled during the evaluation.

<sup>a</sup> Includes persistence based on NostraData average time between scripts.

<sup>b</sup> Assumed 100% compliance.

<sup>c</sup> Assumed 50:50 distribution between 40mg and 80mg strengths.

<sup>d</sup> Assumed all scripts for 80mg strength.

6.28 The redacted table above shows the estimated number of prescriptions of lurasidone is less than 10,000 per year and the financial implications are estimated to be a cost saving in each year.

6.29 The evaluation considered that it was unlikely that the resubmission's estimated savings will be realised as uptake from and substitution of other (cheaper) antipsychotics have not been included.

6.30 The translation of ziprasidone and aripiprazole utilisation to lurasidone scripts relied on the equi-effective dose of lurasidone as calculated in Section D of the submission.

6.31 Given that 80mg is the highest strength of lurasidone proposed for listing and that there is an uncertain dose response between the 40mg and 120mg dose regimens, a

substantial proportion of patients may be taking two tablets to achieve the prescribed dose. This is not accounted for in the estimates of financial implications.

- 6.32 The PBAC noted that there is risk of lurasidone being used outside the proposed indication (e.g. bipolar disorder). Therefore, the PBAC considered that it may be appropriate for a Risk Sharing Arrangement (RSA) with a financial cap to be implemented based on utilization estimates recalculated to take into account changes proposed by the Committee.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of lurasidone on the basis that it should be available as an Authority Required (STREAMLINED) listing on the General Schedule. In making its recommendation, the PBAC considered that lurasidone should be cost-minimised to ziprasidone only.
- 7.2 The PBAC considered that the equi-effective doses are lurasidone 80mg: ziprasidone 114.15mg, calculated relative to the common comparator, olanzapine.
- 7.3 The PBAC agreed with the Secretariat that lurasidone should have the same restriction as for ziprasidone for the treatment of schizophrenia. The PBAC considered that the restriction as proposed in the submission inappropriately differentiates lurasidone from other PBS listed anti-psychotic therapies, noting that currently the only anti-psychotic therapy PBS listed for schizophrenia with a differentiated restriction is clozapine.
- 7.4 Based on international utilisation data, the PBAC considered the dose of lurasidone is unlikely to exceed the available doses of either 40mg or 80mg daily. Therefore, the PBAC agreed that the requested maximum quantity and number of repeats are appropriate.
- 7.5 The PBAC considered that lurasidone will most likely be used in patients who initially achieve a clinical response from treatment with other antipsychotics, but who then switch to lurasidone once stabilised in order to manage weight gain. The PBAC considered it is unlikely that lurasidone will be used as second line therapy in non-responders or that lurasidone will substitute for clozapine.
- 7.6 The PBAC considered that the main comparator is ziprasidone as previously advised (March 2014 Minutes, para.5.1-5.2). The PBAC did not agree that a mixed comparator of aripiprazole and ziprasidone was appropriate. Ziprasidone and lurasidone belong to the same pharmacological class whereas aripiprazole belongs to a different pharmacological class. There is additionally no data to establish a distinct group of patients in whom ziprasidone or aripiprazole, but not the other, is appropriate.

- 7.7 The PBAC accepted that lurasidone is non-inferior in terms of efficacy and safety compared with ziprasidone.
- 7.8 The PBAC noted that compared to olanzapine, lurasidone may have an inferior efficacy profile but a superior safety profile with respect to weight gain and metabolic adverse effects, specifically noting that patients who experience weight gain while on olanzapine appear to lose excess weight upon switching to lurasidone. However, Trial 231 may not have been adequately powered for an active treatment comparison.
- 7.9 The PBAC noted that the dose response of lurasidone was unclear, as there appears to be little difference in effect between 40mg and 120mg doses.
- 7.10 The PBAC noted that it was inappropriate to conduct the cost-minimisation analysis against the mixed comparator of aripiprazole and ziprasidone, as aripiprazole is not considered a relevant comparator.
- 7.11 The PBAC noted that the financial estimates would need to be recalculated to take into account the basis upon which lurasidone is recommended for listing. The PBAC also considered that in the context of estimated use and financial implications, it was difficult to determine what therapies are likely to be replaced by lurasidone. The PBAC noted that the financial estimates did not include other cheaper antipsychotics, and therefore the savings estimated by the submission are unlikely to be realised.
- 7.12 The PBAC considered that it may be appropriate to review the total price paid by Government for anti-psychotic therapies as prices of some of these medicines have been changed.
- 7.13 Advice to the Minister under subsection 101(3BA) of the Act  
In accordance with subsection 101 (3BA) of the Act the PBAC advised that it is of the opinion that lurasidone should be treated as interchangeable on an individual patient basis with ziprasidone.
- 7.14 Similar to ziprasidone's restriction for the treatment of schizophrenia, the PBAC advised that lurasidone is suitable for prescribing by nurse practitioners under a shared care model.
- 7.15 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

**Outcome:**

Recommended

**8 Recommended listing**

- 8.1 Add new item:

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
LURASIDONE Tablet, 40mg, 30 Tablet, 80mg, 30	1	5	Latuda® Dainippon Pharma Ltd Sumitomo

Category / Program	GENERAL – General Schedule
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
Episodicity:	-
Severity:	-
Condition:	Schizophrenia
PBS Indication:	Schizophrenia
Treatment phase:	-
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
Treatment criteria:	-
Clinical criteria:	-
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
Administrative Advice	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.
Cautions	-

## 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.