

**5.2 ARIPIPRAZOLE,
300 mg injection: modified release [1 x 300 mg vial]
(&) inert substance diluent [2 x 3 mL syringe],
400 mg injection: modified release [1 x 400 mg vial]
(&) inert substance diluent [2 x 3 mL syringe],
Abilify Maintena®, Lundbeck Australia Pty Ltd.**

1 Purpose of Application

1.1 To request an Authority required (STREAMLINED) listing for the treatment of schizophrenia.

2 Requested listing

2.1 The submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	DPMQ
ARIPIPRAZOLE 300mg injection: modified release [1 x 300 mg vial] (&) inert substance diluent [2 x 3 mL syringe]	1	5	\$352.06
ARIPIPRAZOLE 400mg injection: modified release [1 x 400 mg vial] (&) inert substance diluent [2 x 3 mL syringe]	1	5	\$433.92

Authority required (STREAMLINED) Schizophrenia
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2.2 Listing was sought on a cost-minimisation basis with paliperidone long acting injection (LAI) as the main comparator.

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

3 Background

3.1 At the time of PBAC consideration, a positive ACPM resolution is available. In June 2014, the ACPM recommended aripiprazole LAI indication “for the maintenance of clinical improvement in the treatment of schizophrenia”.

3.2 Aripiprazole LAI has not been previously considered by the PBAC.

4 Clinical place for the proposed therapy

4.1 Schizophrenia is a severe, chronic, relapsing psychiatric illness with a lifetime prevalence of approximately one percent worldwide. The illness is characterised by disturbances in speech, perception, cognition, volition and emotion.

4.2 Aripiprazole LAI provides an alternative treatment to the currently listed atypical LAI antipsychotics.

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

5 Comparator

- 5.1 The submission nominated paliperidone LAI as the main comparator. Aripiprazole tablets and risperidone LAI were nominated as secondary comparators.
- 5.2 The ESC considered paliperidone LAI, risperidone LAI and olanzapine LAI to be relevant comparators. The ESC noted the submission’s claim that based on recent prescription data (October 2013 – January 2014), paliperidone LAI is the most commonly used atypical LAI antipsychotic.
- 5.3 The ESC further noted that aripiprazole tablets are nominated because of the availability of a direct head-to-head trial of the tablet and LAI formulations. It should also be noted that risperidone LAI, and olanzapine LAI were PBS listed using a relativity of 1:1.79 versus their respective oral tablets.

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 individuals (2), health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with aripiprazole LAI including better social and occupational performance, fewer side effects, decreased risk of relapse etc.

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

Clinical trials

- 6.3 The submission presented two randomised placebo controlled trials (ASPIRE US trial and Hough 2010 trial) for an indirect comparison of aripiprazole LAI and paliperidone LAI and a direct comparison of aripiprazole LAI and aripiprazole tablets, with the treatments used as maintenance therapy.
- 6.4 Supportive comparisons of aripiprazole LAI versus risperidone LAI in the maintenance setting, and aripiprazole LAI versus paliperidone LAI and risperidone LAI in the acute setting were also presented in the submission.
- 6.5 A summary description of the published trials presented in the submission is shown in the table below.

Trial ID/ First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
ASPIRE EU		

Fleischhacker	Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study.	<i>B J Psych</i> 2014, 205:135-144.
Fleischhacker	Personal and social performance in schizophrenia: Double-blind, non-inferiority study of once-monthly vs oral aripiprazole.	<i>Eur Neuropsychopharmacol</i> 2013,23:S474-S475
Peters-Strickland	Aripiprazole once-monthly for schizophrenia: A double-blind, randomised, non-inferiority study versus oral aripiprazole.	<i>Eur Neuropsychopharmacol</i> 2013,23:S473-S474
Fleischhacker	Aripiprazole once-monthly for the treatment of schizophrenia: A double blind, randomized, non-inferiority study vs. oral aripiprazole.	<i>Schizophr Bull</i> 2013,39:S330
Fleischhacker	Aripiprazole Once-monthly for the Treatment of Schizophrenia: A Double-blind, Randomized, Non-inferiority Study vs. Oral Aripiprazole.	<i>Neuropsychopharmacology</i> 2012,38:S339

Indirect comparison of aripiprazole LAI and paliperidone LAI in maintenance setting using placebo common reference

Aripiprazole IM

ASPIRE US		
Kane	Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: A 52-week, multicentre, randomised, double-blind, placebo controlled study.	<i>J Clin Psychiatry</i> 2012, 73(5): 617-624.
Baker	Psychological and overall effectiveness of aripiprazole once-monthly vs. placebo once-monthly for maintenance treatment in schizophrenia.	<i>European Psychiatry</i> 2013, 28(Suppl 1): 2281.
Eramo	A placebo-controlled study of efficacy and safety of aripiprazole once-monthly for long-term maintenance treatment in schizophrenia.	<i>European Psychiatry</i> 2013, 28(Suppl 1): 2277.
Fleischhacker	Long-term safety and tolerability of aripiprazole once-monthly in maintenance treatment of patients with schizophrenia.	<i>Int Clin Psychopharmacol</i> 2013,28(4):171-6.
Loze	Psychosocial and overall effectiveness of aripiprazole intramuscular depot vs. placebo for maintenance treatment in schizophrenia.	<i>Psychotic disorders and antipsychotics</i> 2012: S328
Sanchez	A placebo-controlled study of efficacy/safety of aripiprazole intramuscular depot for long-term maintenance treatment of schizophrenia.	<i>Psychotic disorders and antipsychotics</i> 2012: S327.

Paliperidone IM

Hough	Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: A randomised double-blind, placebo-controlled study.	<i>Schizophrenia research</i> 2010, 116: 107-117.
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Indirect comparison of aripiprazole LAI and paliperidone LAI in acute setting using placebo common reference

Gopal	Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study.	<i>Int Clin Psychopharmacol</i> 2010; 25:247-256.
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Kramer	Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study.	<i>Int J Neuropsychopharmacol</i> 2010; 13:635-47.
Nasrallah	A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia.	<i>Neuropsychopharmacol</i> 2010; 35:2072-82.
Pandina	A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia.	<i>J Clin Psychopharmacol</i> 2010; 30(3):235-244.
Indirect comparison of aripiprazole LAI and risperidone LAI in acute setting using placebo common reference		
NCT00253136		
Kane	Long-acting injectable risperidone: Efficacy and safety of the first long-acting atypical antipsychotic.	<i>American Journal of Psychiatry</i> , v. 160, no. 6, p. 1125-1132.
Kane	Long-acting injectable risperidone: Efficacy and safety.	<i>European Neuropsychopharmacology; 15th. International Congress of the European College of Neuropsychopharmacology, Conference abstract October 5 9., Barcelona, Spain</i> , v. 12, p. S325.
Lauriello	Long-acting risperidone vs. placebo in the treatment of hospital inpatients with schizophrenia.	<i>Schizophrenia Research</i> , v. 72, no. 2-3, p. 249-258.
Nasrallah	Health-related quality of life in patients with schizophrenia during treatment with long-acting, injectable risperidone.	<i>The Journal of clinical psychiatry</i> , v. 65, no. 4, p. 531-536.
Comparison of aripiprazole tablets and risperidone LAI in maintenance setting using aripiprazole tablets common reference		
Macfadden	A Prospective Study Comparing the Long-term Effectiveness of Injectable Risperidone Long-acting Therapy and Oral Aripiprazole in Patients with Schizophrenia.	<i>Psychiatry (Edgemont)</i> 2010;7(11):23–31.
de Arce Cordón	Descriptive analyses of the aripiprazole arm in the risperidone long-acting injectable versus quetiapine relapse prevention trial (ConstaTRE).	<i>Eur Arch Psychiatry Clin Neurosci.</i> 2012 Mar;262(2):139-49.

6.6 Key features of the included evidence – indirect comparison of aripiprazole LAI and paliperidone LAI were shown in the table below.

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Aripiprazole LAI vs. placebo					
ASPIRE US	ARI: 269 PBO: 134	R, DB, MC Median treatment duration ARI: 113 days; PBO: 57 days	Low	Patients with schizophrenia on stable dose of aripiprazole LAI	Relapse, PANSS
Paliperidone LAI vs. placebo					
Hough 2010	PP: 205 PBO: 203	R, DB, MC Median treatment duration PP: 171 days; PBO: 105 days	Low	Patients with schizophrenia on stable dose of paliperidone LAI	Relapse, PANSS

Abbreviations: ARI=aripiprazole; DB=double-blind; LAI=long acting injection; MC=multi-centre; PANSS=positive and negative syndrome scale; PBO=placebo; PP=paliperidone; R=randomised.

- 6.7 The Hough 2010 trial was terminated early because of positive results of an interim analysis. Limited results for the interim analysis, which is the primary analysis, are available.
- 6.8 The inclusion and exclusion criteria, and the demographics and disease characteristics for subjects randomised in the ASPIRE US and Hough 2010 trials are broadly similar. The key differences between the trials are the treatment duration and definition of relapse. The dose of paliperidone LAI in Hough 2010 differs from that recommended in the PI and the average dose (83 mg) appears to be low compared to Australian clinical practice (103 mg). The relatively low dose may bias the comparison against paliperidone LAI.
- 6.9 The proportion of relapsed patients differed in the placebo arms of the 2 trials, and the median time to relapse was longer in ASPIRE US. This may reflect different relapse definitions and/or other unidentified differences in the patient populations or trial designs.
- 6.10 The ESC noted the Pre-Sub-Committee Response (PSCR p1) argues that the impact of the different treatment durations across the trials may be mitigated by the follow-up for the placebo group in the ASPIRE US trial being relatively short and the calculated hazard ratios remaining constant for the duration of follow-up, although the longer follow-up observed in Hough confers a comparative ascertainment advantage on to the paliperidone LAI comparator arm of the subsequent indirect comparison. The ESC also noted in the PSCR (p1) that expert opinion included in the submission that outcomes for the two trials are comparable even though the definitions of relapse differed slightly. The ESC considered these arguments are reasonable and that there is reasonable similarity when comparing the common reference of placebo in this indirect comparison.
- 6.11 Key features of the included evidence – direct comparison of aripiprazole LAI and aripiprazole tablets were shown in the table below.

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Aripiprazole LAI vs. aripiprazole tablets					
ASPIRE EU	ARI LAI 400 mg: 265 ARI tablets: 266 ARI LAI 50 mg: 131	R, DB, MC 38 weeks	Low	Patients with schizophrenia on stable dose of aripiprazole tablets	Relapse, Response, Remission, PANSS

Abbreviations: ARI=aripiprazole; DB=double-blind; LAI=long acting injection; MC=multi-centre; PANSS=positive and negative syndrome scale; PLB=placebo; R=randomised.

- 6.12 The primary endpoint and non-inferiority margin for the ASPIRE EU trial were changed mid-trial, but prior to unblinding, because of a lower than expected relapse rate.

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

Comparative effectiveness

- 6.13 Results of relapse and PANSS total scores across the randomised trials used in the indirect comparison are shown in the table below.

Trial ID	ASPIRE US			Hough 2010			Indirect estimate of effect ^c
	Treatment effect ^a	Aripiprazole LAI	Placebo	Placebo	Paliperidone LAI	Treatment effect ^b	
Time to relapse							
	HR (95% CI)	median	median	median	median	HR (95% CI)	Indirect HR (95% CI)
ASPIRE US, final analysis	0.199 (0.125, 0.317)	N=269 Not reached	N=134 209 days				-
Hough 2010, final analysis				N=203 172 days	N=205 Not reached	0.278 (0.189, 0.408)	0.716 (0.391, 1.309)
Proportion of subjects experiencing relapse							
	Tmt effect ^a (95% CI)	n with event/N (%)	n with event/N (%)	n with event/N (%)	n with event/N (%)	Tmt effect ^b (95% CI)	Indirect (95% CI)
ASPIRE US, final analysis	RR: 0.25 (0.17, 0.38) RD: -0.30 (-0.39, -0.20)	27/269 (10.0)	53/134 (39.6)				
Hough 2010, final analysis				97/203 (47.8)	36/205 (17.6)	RR: 0.37 (0.26, 0.51) RD: -0.30 (-0.39, -0.22)	RR: 0.68 (0.40, 1.14) RD: 0.00 (-0.13, 0.13)
Mean change in PANSS total score							
	RD (95% CI)	Mean change from baseline (SD)	Mean change from baseline (SD)	Mean change from baseline (SD)	Mean change from baseline (SD)	RD (95% CI)	Indirect RD (95% CI)
ASPIRE US, final analysis	-10.11 (-12.68, -7.54)	N=266 Baseline: 54.4 1.43 (12.3)	N=134 Baseline: 54.4 11.55 (12.3)				
Hough 2010, final analysis				N=203 Baseline: 53.0 11.1 (16.6)	N=205 Baseline: 52.0 2.5 (12.2)	-8.60 (-11.43, -5.77)	-1.51 (-5.33, 2.31)

^a proposed drug over common reference; ^b main comparator over common reference; ^c inferred as proposed drug over main comparator.

Abbreviations: CI=confidence interval; HR=hazard ratio; *n*=number with event; *N*=number in group; OR=odds ratio; RD=risk difference; RR=relative risk; SD=standard deviation

Source: Table 62, p173, Table 63, p176, Table 64, p181 of the submission, Table 9.3-1, p214 of trial report, Table 1 of 004198 Trial Synopsis;

- 6.14 The upper 95% CI for the indirect comparisons are below the non-inferiority margins previously accepted by the PBAC although these margins were for direct comparisons (20% difference in relapse rates [olanzapine LAI PSD, July 2009] and 5-7 point difference in PANSS total score [paliperidone LAI PSD, November 2010]). The upper 95% CI for the time to relapse (1.309) is below the non-inferiority margin for ASPIRE EU (1.68). The upper 95% CI for the proportion relapsed is below the non-inferiority margin for ASPIRE EU (11.5%) using the interim results for Hough 2010 (7%) but not using the final results (13%).
- 6.15 Results of relapse, response, remission and PANSS total scores across the direct randomised trial are shown in the table below.

Outcome	Aripiprazole LAI 400 mg	Aripiprazole tablets	RD (95% CI)	HR (95% CI)
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Estimated proportion relapsed by end of week 26 (KM estimates)	7.12% ^a (SE 1.6%) N=265, number at risk at week 26=215 (81%)	7.76% ^a (SE 1.72) N=266, number at risk at week 26=201 (76%)	-0.01 (-0.05, 0.04)	HR for time to relapse: 0.991 (0.545, 1.803)
	n with event/N (%)	n with event/N (%)	RD (95% CI)	RR (95% CI)
Overall relapse rate	22/265 (8.30)	21/266 (7.89)	0.00 (-0.04, 0.05)	1.05 (0.59, 1.87)
	Baseline score; Endpoint LS mean change (SE)	Baseline score; Endpoint LS mean change (SE)	RD (95% CI)	p-value
PANSS total score	57.94; -1.66 (0.718)	56.57; 0.58 (0.714)	-2.24 (-4.23, -0.25)	0.0272

Abbreviations: HR=hazard ratio; LS=least squares; RD=risk difference; RR=relative risk; SE=standard error
Source: Table 22, p111, Table 23, p113, Table 24, p115, Table 25, p116, Table 26, p117 of the submission.

- 6.16 The upper 95% CI for the difference in the proportion relapsed (4%) was below the non-inferiority margin (11.5%). The proportion of relapsed subjects for the aripiprazole LAI 400 mg group (7.12%) was significantly lower than that in the aripiprazole LAI 50 mg group (21.8%; $p = 0.0006$). Thus assay sensitivity was confirmed. The time to relapse was similar in the aripiprazole LAI 400 mg and the aripiprazole tablet arms. However, the upper 95% CI for the HR (1.80) is above the non-inferiority margin (1.68).

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

Comparative harms

- 6.17 A summary of key adverse events in the direct randomised trials included in the indirect comparison is shown in the table below.

	ASPIRE US			Hough 2010		
	<i>Stabilisation</i>	Double-blind phase		<i>Maintenance</i>	Double-blind phase	
	<i>ARI LAI</i> n with event/N (%)	<i>ARI LAI</i> n with event/N (%)	<i>PBO</i> n with event/N (%)	<i>PP LAI</i> n with event/N (%)	<i>PP LAI</i> n with event/N (%)	<i>PBO</i> n with event/N (%)
Any TEAE	345/576 (59.9)	170/269 (63.2)	83/134 (61.9)	569/849 (67)	91/205 (44.4)	91/203 (44.8)
Serious TEAE	25/576 (4.3)	11/269 (4.1)	9/134 (6.7)	116/849 (14)	11/205 (5.4)	26/203 (12.8)
TEAE leading to withdrawal	28/576 (4.9)	19/269 (7.1)	18/134 (13.4)	52/849 (6)	3/205 (1.5)	1/203 (0.5)
Injection site pain	34/576 (5.9)	8/269 (3.0)	5/134 (3.7)	NR	NR	NR
Weight increase	40/576 (6.9)	26/269 (9.7)	13/134 (9.7)	~6.5%	15/205 (7.3)	2/203 (1.0)
Any EPS or EPS-related event	75/576 (13.0)	40/269 (14.9)	13/134 (9.7)	9%	6%	2%
Anti-EPS medications ^a	98/576 (17.0)	45/269 (16.7)	14/134 (10.4)	12%	10%	6%
Prolactin-related AEs	23/564 (4.1)	5/257 (1.9)	9/126 (7.1)	3%	2%	1%

^a anticholinergics for the ASPIRE US trial. Abbreviations: AEs=Adverse events; EPS=extrapyramidal symptoms; NR=not reported; TEAE=treatment emergent adverse event Source: See Table B(i).6.2 of Commentary.

- 6.18 The incidence of treatment emergent adverse events (TEAEs) was similar in the active and placebo arms of each trial, although the overall incidence was lower in

Hough 2010. In each trial the incidence of serious TEAEs and TEAEs leading to discontinuation were similar or lower for the active arms compared with the placebo arms.

- 6.19 The incidence of extrapyramidal symptoms (EPS) or EPS-related events, and the use of medications for the treatment of EPS, were higher in the active treatment arms compared with the placebo arms. In ASPIRE US akathisia was the most common EPS event.
- 6.20 A summary of key treatment adverse events in the direct randomised trials is shown in the table below.

Event	Aripiprazole LAI 400 mg n with event/N (%)	Aripiprazole tablets n with event/N (%)	Aripiprazole LAI 50 mg n with event/N (%)
Any TEAE	219/265 (82.6)	213/266 (80.1)	106/131 (80.9)
Serious TEAE	15/265 (5.7)	15/266 (5.6)	11/131 (8.4)
TEAE leading to withdrawal	21/265 (7.9)	19/266 (7.1)	24/131 (18.3)
Injection site pain	20/265 (7.5)	6/266 (2.3)	1/131 (0.8)
Weight increase	24/265 (9.1)	31/266 (13.2)	7/131 (5.3)
Any EPS or EPS-related event	58/265 (21.9)	31/266 (11.7)	16/131 (12.2)
Anticholinergic agents	52/265 (19.6)	46/266 (17.3)	18/131 (13.7)
Prolactin, mean change (SD)	-0.33 (3.07)	0.79 (5.30)	1.11 (3.64)

Abbreviations: EPS=extrapyramidal symptoms; LS=least squares; SD=standard deviation; TEAE=treatment emergent adverse event. Source: See Table B.6.2 of the Commentary.

- 6.21 The incidence of TEAEs and serious TEAEs was similar in the 3 treatment arms. The incidence of TEAEs leading to discontinuation was lower in the aripiprazole LAI 400 mg and aripiprazole tablet arms compared with the low dose aripiprazole LAI arm.
- 6.22 The incidence of injection site pain was higher in the aripiprazole LAI 400 mg arm compared with the aripiprazole tablet and low dose aripiprazole LAI arms. Weight increase was more common with aripiprazole tablets compared with aripiprazole LAI 400 mg. The incidence of EPS or EPS-related events, and the use of medications for the treatment of EPS, were higher in the aripiprazole LAI 400 mg arm compared with the aripiprazole tablet and low dose aripiprazole LAI arms. Akathisia was the most common EPS event. The TGA Clinical Evaluator noted that suicidal ideation/suicide appeared greater (1.1%) with aripiprazole LAI 400/300mg than with aripiprazole tablets (0.4%).
- 6.23 A summary of the comparative benefits and harms for aripiprazole LAI versus paliperidone LAI is presented in the table below.

Benefits					
Time to relapse					
ASPIRE US	Aripiprazole LAI	PBO	Absolute Difference	HR (95% CI)	
Relapsed*	27/269	53/134	-0.30 (-0.39, -0.20)		
Median (days)	Not reached	209		0.199 (0.125, 0.317)	
Hough 2010	Paliperidone LAI	PBO	Absolute Difference	HR (95% CI)	
Relapsed*	97/203	36/205	-0.30 (-0.39, -0.22)		
Median (days)	Not reached	172		0.278 (0.189, 0.408)	
Indirect comparison: ASPIRE US vs Hough 2010			0.00 (-0.13, 0.13)	0.716 (0.391, 1.309)	
Harms					
	Active	PBO	RR (95% CI)	Event rate/100 patients*	RD

				Active	PBO	(95% CI)	
Any EPS or EPS-related event							
ASPIRE (ARI LAI)	US	40/269	13/134	1.53 (0.85, 2.77)	14.9	9.7	0.05 (-0.01, 0.12)
Hough (PP LAI)	2010	12/205 ^a	4/203 ^a	2.97 ^a (0.97, 9.06)	6	2	0.04 ^a (0.00, 0.08)
Weight increase							
ASPIRE (ARI LAI)	US	26/269	13/134	1.00 (0.53, 0.88)	9.7	9.7	0.00 (-0.06, 0.06)
Hough (PP LAI)	2010	15/205	2/203	7.43 (1.72, 32.06)	7.3	1.0	0.06 (0.03, 0.10)

* Median duration of exposure: ASPIRE US ARI LAI=113 days, PBO=57 days; Hough 2010 PP LAI=171 days, PBO=105 days a estimated from percentage reported in Hough 2010. Abbreviations: ARI = aripiprazole; PBO = placebo; PP = paliperidone; RD = risk difference; RR = risk ratio. Source: Compiled during the evaluation.

- 6.24 Based on an indirect comparison using placebo as the common comparator, the ESC considered that aripiprazole LAI appears to be no worse than paliperidone LAI in the maintenance treatment of schizophrenia.
- 6.25 On the basis of the indirect comparison, the ESC considered that the frequency of adverse effects appears to be the same for the two treatments.
- 6.26 A summary of the comparative benefits and harms for aripiprazole LAI versus aripiprazole tablets from ASPRE EU is presented in the table below.

Aripiprazole LAI	Aripiprazole tablets	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
			Aripiprazole LAI	Aripiprazole tablets	
Benefits					
Proportion with relapse					
Overall: 22/265	Overall: 21/266	HR: 0.991 (0.545, 1.803)	Week 26: 7.12%	Week 26: 7.76%	-0.01 (-0.05, 0.04)
Harms					
Injection site pain					
20/265	6/266	3.35 (1.37, 8.20)	7.5	2.3	0.05 (0.02, 0.09)
Any EPS or EPS-related event					
58/265	31/266	1.88 (1.26, 2.81)	21.9	11.7	0.10 (0.04, 0.17)

* Maximum duration of follow-up: 38 weeks. Abbreviations: CI=confidence interval; HR=hazard ratio; RD = risk difference; RR = risk ratio. Source: Compiled during the evaluation.

- 6.27 On the basis of the head to head trial, the ESC considered that aripiprazole LAI appears to have the same effect as aripiprazole tablet in the maintenance treatment of schizophrenia.
- 6.28 On the basis of the head to head trial presented, the ESC considered that the frequency of adverse effects appears to be the same for the two treatments.

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

Clinical claim

- 6.29 The submission describes aripiprazole LAI as non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over the main comparator paliperidone LAI, and the secondary comparators aripiprazole tablets and risperidone LAI.

- This claim is adequately supported for the comparison with paliperidone LAI in the maintenance setting, although it is based on an indirect comparison and as noted above there are differences across the trials.
- This claim is adequately supported for the efficacy comparison with aripiprazole tablets in the maintenance setting. In terms of safety, the frequency of adverse effects appears to be the same for the two treatments.
- This claim is not adequately supported for the comparison with risperidone LAI in the maintenance setting. The comparison with risperidone (detailed in Attachment B_1 of the Commentary) is not reliable given differences across the trials potentially invalidating an indirect comparison. The PBAC did not consider this to be crucial to PBAC consideration given paliperidone LAI was recommended on the basis of cost-minimisation to risperidone LAI, and non-inferiority with paliperidone LAI is the main claim of this aripiprazole LAI submission.
- This claim is not adequately supported for the indirect comparisons versus paliperidone LAI and risperidone LAI in the acute setting due to substantial differences across the trials.

6.30 Overall, the ESC considered that aripiprazole LAI is non inferior in terms of efficacy and safety compared to paliperidone LAI and aripiprazole tablet in the maintenance treatment of schizophrenia.

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

Economic analysis

- 6.31 The requested prices for aripiprazole LAI are based on a 1:1.79 relative price advantage over aripiprazole tablets. The justification provided in the submission for this approach is that olanzapine LAI, risperidone LAI and haloperidol LAI were priced with a 1:1.79 price advantage over the oral formulations (Olanzapine PSD, July 2009).
- 6.32 The ESC noted that paliperidone LAI was not priced based on the tablet formulation and instead was cost minimised versus risperidone LAI. The PBAC should consider whether the 1:1.79 price advantage is applicable to aripiprazole LAI.
- 6.33 The equi-effective doses are estimated as aripiprazole LAI 389.61 mg every 28 days and aripiprazole tablets 20.0 mg daily. The dose for aripiprazole tablets is from the ASPIRE EU head-to-head trial whereas the dose for aripiprazole LAI is from the ASPIRE US trial. Using the aripiprazole LAI dose from the ASPIRE EU trial, the equi-effective doses are estimated as aripiprazole LAI 393.2 mg every 28 days and aripiprazole tablets 20.0 mg daily.
- 6.34 In the submission the price advantage is applied to the dispensed prices and hence the premium is applied to the fixed pharmacy mark-up (\$18) and dispensing fee (\$6.63).
- 6.35 During the evaluation the equi-effective doses were estimated as aripiprazole LAI 390 mg and paliperidone LAI 83 mg.
- 6.36 For the paliperidone LAI PBAC submission the equi-effective doses for paliperidone LAI and risperidone LAI were sourced from market data due to the trial data not representing steady state doses and the proportion of patients switching from oral antipsychotics (and hence requiring paliperidone loading doses) being unknown. Using the average paliperidone LAI dose calculated from Medicare Australia PBS

data, the estimated equi-effective doses are aripiprazole LAI 390 mg and paliperidone LAI 103 mg.

6.37 Ex-manufacture prices per aripiprazole LAI injection is presented in the table below.

Scenario	300 mg strength ^a	400 mg strength ^a
1:1.79 price premium for aripiprazole LAI compared with aripiprazole tablets		
As presented in the submission	\$304.53	\$380.66
Using ex-manufacturer prices	\$288.70	\$360.87
Using aripiprazole LAI dose from ASPIRE EU (393.2 mg/28 days) and ex-manufacturer prices	\$286.69	\$358.36
Cost-minimisation analysis for aripiprazole LAI and paliperidone LAI		
Equi-effective doses from indirect comparison of ASPIRE US (aripiprazole LAI 390 mg every 28 days) and Hough 2010 (paliperidone LAI 83 mg every 28 days)	\$232.36	\$290.45
Equi-effective doses from ASPIRE EU for aripiprazole LAI (390 mg every 28 days) and Medicare Australia PBS statistics for paliperidone LAI (103 mg every 28 days)	\$288.06	\$360.08

^a The relative use of the 300 mg and 400 mg doses of aripiprazole LAI is from the ASPIRE US trial and the price of the 400 mg strength is 1.25 times the price of the 300 mg strength. Source: Compiled during evaluation.

6.38 The above prices do not include the cost of oral aripiprazole for the first 14 days when initiating aripiprazole LAI. The average treatment duration with aripiprazole LAI, and hence the number of aripiprazole LAI prescriptions over which the cost of the oral aripiprazole should be apportioned, is unknown. An average oral aripiprazole cost per aripiprazole LAI prescription of \$1.35 (oral dose of 10 mg; average LAI treatment duration of 7 years) to \$6.73 (15 mg; 2 years) was estimated during the evaluation. If more than 32% of patients switch from oral antipsychotics to paliperidone LAI, the cost of the paliperidone LAI loading doses will be greater than the cost of the concomitant oral aripiprazole.

6.39 Drug cost for each patient using aripiprazole LAI per year will be from \$4,577 (300 mg) to \$5,641 (400 mg). Drug cost for each patient using paliperidone LAI per year will be from \$1,948 (25 mg) to \$5,732 (100 or 150 mg).

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

Estimated PBS usage & financial implications

6.40 Estimated PBS usage and financial implications are presented in the table below.

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Atypical LAI scripts	185,775	192,647	199,142	205,310	211,192
Aripiprazole LAI market share	11%	18%	21%	23%	26%
Aripiprazole LAI scripts	20,088	34,979	41,192	47,948	53,959
Estimated net cost to PBS/RPBS					
Net cost to PBS for aripiprazole LAI (including concomitant oral aripiprazole)	\$8,774,095	\$14,921,634	\$17,370,499	\$20,210,985	\$22,716,339
Net cost to PBS for substituted therapies	\$7,692,031	\$13,506,345	\$16,018,932	\$18,761,623	\$21,227,691
Estimated total net PBS/RPBS cost	\$1,082,065	\$1,415,289	\$1,351,566	\$1,449,362	\$1,488,648

Source: Table 87 p222, Table 90 p224 and Table 91 p232 of the submission

6.41 In year 5 the additional cost for aripiprazole LAI of \$1,488,648 is due to:

- the cost of concomitant oral aripiprazole when initiating aripiprazole LAI

- (\$313,120);
 - the higher average prescription cost for aripiprazole LAI vs paliperidone LAI $((\$415.19 - \$393.30) \times 40,655 \text{ prescriptions} = \$889,848)$;
 - the higher average prescription cost for aripiprazole LAI vs risperidone LAI $((\$415.19 - \$352.49) \times 11,288 \text{ prescriptions} = \$704,050)$; and
 - the lower average prescription cost for aripiprazole LAI vs olanzapine LAI $((\$415.19 - \$616.70) \times 2,076 \text{ prescriptions} = -\$418,370)$.
- 6.42 The submission's estimates of the PBS costs are likely to be underestimated because:
- growth in the LAI market has potentially been underestimated (increasing the uptake of aripiprazole LAI by 25% or increasing the growth in the total LAI market increases the net PBS/RPBS cost in year 5 by \$372,196 and \$465,765, respectively);
 - the cost savings associated with olanzapine replacement have been overestimated due to assuming the 300 mg strength is dosed fortnightly whereas it can also be dosed monthly (assuming all of the 300 mg strength of olanzapine LAI is dosed monthly increases the net PBS/RPBS cost in year 5 by \$344,626);
 - the number of new patients treated with aripiprazole LAI each year has possibly been underestimated and some patients are likely to be treated with higher than a 10 mg dose of oral aripiprazole (assuming 3,082 new patients are treated with aripiprazole LAI each year, and all patients are treated with 15 mg oral aripiprazole, increases the net PBS/RPBS cost in year 5 by \$306,609); and
 - substitution for less expensive oral atypical antipsychotics is not considered.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of aripiprazole on a cost-minimisation basis compared to paliperidone LAI, as an Authority required (STREAMLINED) listing for the treatment of schizophrenia.
- 7.2 The PBAC noted the TGA Delegate's decision to recommend aripiprazole for the 'maintenance treatment of schizophrenia where clinically appropriate'. However the PBAC considered that it is reasonable to assume that prescribers would be unlikely to initiate patients on the modified release injection formulation and therefore a listing simply for "schizophrenia" is appropriate and consistent with other PBS-listed modified release antipsychotic injections.
- 7.3 The PBAC agreed with the submission that based on recent prescription data (October 2013 – January 2014), paliperidone LAI is the most commonly used atypical LAI antipsychotic and further accepted that paliperidone LAI is the appropriate main comparator.
- 7.4 Based on the indirect comparison provided with placebo as common reference (ASPIRE-US and Hough 2010), the PBAC accepted that treatment with aripiprazole resulted in mean changes in PANSS scores that were comparable to those associated with paliperidone LAI.
- 7.5 In terms of safety, the PBAC noted the higher incidences of extrapyramidal symptoms (EPS) or EPS-related events with aripiprazole LAI compared to aripiprazole tablets and weight increase was more common with aripiprazole tablets compared

with aripiprazole LAI. Overall, compared to the main comparator, paliperidone LAI, PBAC considered the safety profiles differed slightly but were comparable.

- 7.6 The PBAC considered that the data presented adequately supported the submission's claims of non-inferior comparative efficacy and safety versus paliperidone LAI albeit with a difference in the safety profile.
- 7.7 The PBAC noted that the requested prices for aripiprazole LAI are based on a 1:1.79 relative price advantage over aripiprazole tablet. However, the PBAC recalled that paliperidone LAI was not priced based on the tablet formulation and instead was cost-minimised versus risperidone LAI (Paliperidone Public Summary Document November 2010 PBAC). PBAC considered cost-minimisation of aripiprazole LAI versus paliperidone LAI to be the most relevant basis for PBS pricing.
- 7.8 The PBAC noted arguments in the Pre-PBAC response (p1) that the use of the average dose used in clinical practice for paliperidone LAI is reasonable considering the equi-effective doses for paliperidone LAI and risperidone LAI were sourced from market data for the purposes of calculating PBS paliperidone prices. The pricing using market data also results in similar pricing to the 1.79 price advantage over aripiprazole tablets. However, PBAC considered the decision in November 2010 for paliperidone LAI took into consideration that the trial data were not at steady state and were immature, which meant the dose relativity at study endpoint may not be informative (Paliperidone Public Summary Document November 2010 PBAC). The head to head trial data versus risperidone LAI presented in the paliperidone LAI submission in November 2010 is different to the Hough 2010 data versus placebo presented in the indirect comparison with aripiprazole LAI in this submission. Given the trial data in this aripiprazole LAI submission represent steady state dosing for both aripiprazole and paliperidone, the equi-effective dosing should be from the trial data (ASPIRE US and Hough 2010) and not sourced from market data. Therefore the PBAC considered that aripiprazole LAI 390 mg every 28 days is equi-effective to paliperidone 83 mg every 28 days.
- 7.9 The PBAC agreed with the ESC that the submission's estimates of utilisation and PBS costs are likely to be underestimated. PBAC also questioned whether the submission's claim that 40% of the paliperidone market will be absorbed by aripiprazole is reliable.
- 7.10 The PBAC recommended that the Safety Net 20 Day Rule should apply.
- 7.11 The PBAC recommended that aripiprazole is suitable for prescribing by nurse practitioners within a shared care model.
- 7.12 The PBAC recommended that aripiprazole LAI should be treated as interchangeable on an individual patient basis with paliperidone LAI and risperidone LAI, according to Section 101(3BA) of the *National Health Act 1953*. The PBAC recommended that aripiprazole should not be treated as interchangeable with olanzapine LAI.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

Name, Restriction, Manner of administration and form	Max Qty	No. of Rpts	Proprietary and Manufacturer	Name
ARIPIPRAZOLE				
aripiprazole 300 mg injection: modified release [1 x 300 mg vial] (& inert substance diluent [1 vial], 1 pack.	1	5	Abilify Maintena	LU
aripiprazole 400 mg injection: modified release [1 x 400 mg vial] (& inert substance diluent [1 vial], 1 pack	1	5		

Category/ Program	GENERAL- General Schedule (Code GE)
Episodicity:	---
Severity:	---
Condition:	Schizophrenia
Restriction:	Authority required (STREAMLINED)
Administrative Advice	<p><u>Note</u> Shared Care Model:</p> <p>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.</p>

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

Lundbeck welcomes the recommendation to add Abilify Maintena to the PBS, but believes the dosage relativity to paliperidone LAI, as determined by the PBAC, is not reflective of clinical practice utilisation of these medicines.

Lundbeck would also like to clarify that in the ASPIRE US trial, the most common EPS event was tremor (rather than akathisia as stated above).