

5.01 ARIPIRAZOLE,

I.M. injection (modified release) 720 mg in 2.4 mL pre-filled syringe,

I.M. injection (modified release) 960 mg in 3.2 mL pre-filled syringe,

Abilify Asimtufii®,

Lundbeck Australia Pty Ltd

1 Purpose of submission

- 1.1 The Category 2 submission requested General Schedule, Authority Required (Streamlined) listings for aripiprazole 2-monthly injection (hereafter described as A2M) for the maintenance treatment of schizophrenia in adults who are stabilised on aripiprazole once monthly injection (AOM).
- 1.2 Listing of A2M was requested on the basis of a cost-minimisation approach versus the existing long acting injectable (LAI) formulation of aripiprazole/AOM (Abilify Maintena).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adults with schizophrenia who are stabilised on AOM (400 mg or 300 mg)
Intervention	A2M 960 mg or 720 mg administered by intramuscular injection
Comparator	AOM 400 mg or 300 mg administered by intramuscular injection
Outcomes	Pharmacokinetic outcomes (aripiprazole plasma concentration) Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression – Severity (CGI-S) Clinical Global Impression – Improvement (CGI-I) Safety
Clinical claim	A2M is non-inferior to AOM in terms of efficacy and safety

Source: Table 1, p22 of the submission; p21 of the submission.

AOM = Aripiprazole once monthly; A2M = Aripiprazole two-monthly

2 Background

Registration status

- 2.1 TGA status at time of PBAC consideration: not registered. The submission was made under the TGA/PBAC Parallel Process, with the TGA Clinical Evaluator’s Round 2 Report available at the time of ESC consideration and the TGA Delegate’s Overview available prior to consideration by the PBAC.
- 2.2 The proposed TGA indications for A2M were:
“For the maintenance treatment of schizophrenia in adults.

For maintenance treatment to prevent the recurrence of manic or mixed episodes of bipolar I disorder in adult patients as monotherapy.”

Previous PBAC consideration

- 2.3 A2M has not previously been considered by the PBAC.
- 2.4 The PBAC previously recommended 7 atypical (“second generation”) LAIs to treat schizophrenia.
- 2.5 Olanzapine LAI every 2-4 weeks, paliperidone LAI once monthly, risperidone once fortnightly, risperidone 4-weekly, and AOM have no PBS clinical eligibility criteria other than “schizophrenia” (risperidone once fortnightly is also PBS listed for Bipolar I disorder).
- 2.6 The listing for paliperidone 3-monthly requires patients to have previously received and been stabilised on paliperidone once monthly for at least 4 consecutive months or at least one paliperidone 6 monthly injection. The listing for paliperidone 6-monthly requires patients to have previously received and been stabilised on paliperidone once monthly for at least 4 consecutive months or at least one paliperidone 3 monthly injection.

3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<i>ARIPIPRAZOLE</i>					
<i>aripiprazole 960 mg/3.2 mL modified release injection, 3.2 mL syringe</i>	NEW	1	1	2	Abilify Asimtufii
<i>aripiprazole 720 mg/2.4 mL modified release injection, 2.4 mL syringe</i>	NEW	1	1	2	Abilify Asimtufii
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new/existing code]					
Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>					
Administrative Advice: <i>No increase in the maximum quantity or number of units may be authorised.</i>					
Administrative Advice: <i>Patient dosage is to be determined as per the Product Information.</i>					
Indication: Schizophrenia					

Clinical criteria:
Patient must have previously received and be stabilised on PBS-subsidised aripiprazole once-monthly injection
Administrative Advice: 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.

- 3.2 The submission did not propose any special pricing arrangements.
- 3.3 The prescribing instructions suggest that Nurse Practitioners may be intended to be included under the Prescriber type given the proposed Shared care model. This is similar to the prescribing instructions for AOM. LAI forms of paliperidone are able to be prescribed by nurse practitioners under these arrangements. Between finalisation of the evaluation and PBAC consideration in December 2024, the listings of aripiprazole were updated to remove the shared care model advice. Therefore, the administrative advice is likely unnecessary for the listing of A2M.
- 3.4 The requested PBS restriction required patients to be stabilised on AOM before receiving A2M, whereas only 4.3% of participants met such a requirement in Trial 031-201-00181.
- 3.5 The proposed PBS restriction included the clinical criterion: “patient must have previously received and be stabilised on PBS subsidised aripiprazole long acting injection”. Unlike the paliperidone 3 monthly and 6 monthly criteria (see paragraph 2.6), a minimum duration of stabilisation was not included. The draft PI states that the first A2M injection may be administered instead of the second or any later injection of AOM (p2 of the draft A2M PI).

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

4 Population and disease

- 4.1 Schizophrenia is a chronic and debilitating relapsing psychiatric disorder characterised by delusions, hallucinations, and thought disorder. It also significantly impacts emotional expression, motivation, social interaction, motor function, and cognition. This disrupts a person's ability to function in daily life, including work, school, and social relationships. Schizophrenia is also associated with an increased risk of cardiovascular disease, highlighting its negative impact on physical health.
- 4.2 Management of schizophrenia in both acute and maintenance phases rely on antipsychotic medications, with atypical (“second generation”) agents being generally preferred. While all antipsychotics target dopamine receptors, individual medications vary in effectiveness, side effects, and formulation. These variations guide the personalised selection of antipsychotics for patients with schizophrenia. Treatment decisions consider disease severity, response history, and tolerability. Therapy aims to

balance medication efficacy, adverse event profiles, patient preferences, and adherence.

- 4.3 Management of acute schizophrenia episodes prioritises rapidly alleviating symptoms and stabilising the individual. Once achieved, LAI (known as depot medications) become an important option for maintenance therapy. Depot injections include a liquid that releases medication slowly over several weeks. Their primary benefit lies in improved medication adherence, a major factor in schizophrenia relapse prevention and reduced re-hospitalisation risk by 20-30% compared to oral medication (Tiihonen 2017)¹.
- 4.4 The main difference between the current and proposed clinical management algorithm was the addition of A2M as an additional maintenance treatment option for patients with schizophrenia who are stable and currently treated with AOM. The submission proposed the following algorithm for transitioning from AOM to A2M:
- For patients stabilised on AOM 400 mg, one injection of A2M 960 mg every 56 days would be administered in place of the next scheduled injection of AOM 400 mg once monthly.
 - For patients stabilised on AOM 300 mg once monthly, one injection of A2M 720 mg once every 56 days would be administered instead of the next scheduled injection of AOM 300 mg once monthly.
 - The first A2M injection could be administered instead of the second or any later injection of AOM.
 - Patients could be administered A2M up to 2 weeks before or 2 weeks after the scheduled 2-month dose.
 - In case of adverse events with A2M 960 mg once every 56 days, a dose reduction to A2M 720 mg once every 56 days could be considered at the time of the next scheduled injection.

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

5 Comparator

- 5.1 The submission nominated AOM as the main comparator.
- 5.2 The main arguments provided in support of nominating AOM as an appropriate comparator for A2M were as follows:
- Pharmacological equivalence: A2M and AOM were considered interchangeable due to their identical active moiety and mechanism of action due to their near-

¹ Australian Institute of Health and Welfare (AIHW). (2022). Australian Burden of Disease Study 2022. Retrieved from <https://www.aihw.gov.au/reports/burden-of-disease/australian-burden-of-disease-study-2022>.

identical pharmacokinetic (PK) profiles. This would translate to similar efficacy and safety profiles, making them suitable for a similar subset of patients.

- TGA PI: The proposed TGA PI for A2M recommended that patients be stabilised on AOM before transitioning to A2M. This would minimise relapse and adverse events due to continued exposure to the same active ingredient. Further, this requirement aligned with the PBS restrictions for other LAIs for schizophrenia, such as paliperidone.
- Treatment continuity: Treatment guidelines recommend continuing with the initial antipsychotic that yielded a positive response in the acute phase (Galletly 2016)². The transition between atypical antipsychotics would typically occur only if new adverse events or tolerability issues arose.

5.3 Under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.4 At its March 2024 meeting, the PBAC recommended risperidone 4 weekly LAI on a cost minimisation basis with the least costly alternative of risperidone 2 weekly LAI, paliperidone LAIs, or aripiprazole 4 weekly LAI (see published PBAC March 2024 Outcomes). It is noted, however, that risperidone 4 weekly LAI does not require patients to be stabilised on risperidone prior to commencing treatment.

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) via the Consumer Comments facility on the PBS website, both supporting the listing of A2M. The Committee noted the input described the effectiveness of aripiprazole and how it helps them remain calm and keep their condition stable but also described the high cost of accessing aripiprazole privately as prohibitive and the need for broader access. The PBAC also noted the input discussed aripiprazole for bipolar disorder (BPD), an

² Galletly, C., Castle, D., et. al. (2016). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. The Australian and New Zealand journal of psychiatry. 50(5), 410–472. <https://doi.org/10.1177/0004867416641195>.

indication for which PBS listing was not presently being sought for A2M.

Clinical trials

- 6.3 The submission was based on one head-to-head randomised trial comparing A2M to AOM in adults with schizophrenia or BP-I disorder. Trial 031-201-00181 included 266 adults with schizophrenia (n=185) or BP-I disorder (n=81).
- 6.4 A claim of non-inferiority was made on (i) the secondary efficacy outcomes captured in Trial 031-201-00181 and (ii) using PK data from the trial as a bridge to efficacy outcomes.
- 6.5 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Trial 031-201-00181 NCT04030143	A Phase 1b, Open-label, Multiple-dose, Randomized, Parallel-arm, Safety, Tolerability, and Pharmacokinetic Trial of Aripiprazole Intramuscular Depot Administered in the Gluteal Muscle in Adult Subjects with Schizophrenia or Bipolar I Disorder.	CSR and protocol, March 2021
	Harlin, M., et al. A Randomized, Open-Label, Multiple-Dose, Parallel-Arm, Pivotal Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Aripiprazole 2-Month Long-Acting Injectable in Adults with Schizophrenia or Bipolar I Disorder.	CNS drugs 2023; 37(4): 337-350
	Citrome, L., et al. Safety and Efficacy of Aripiprazole 2 month ready to use 960 mg: Secondary Analysis of Outcomes in Adult Patients with Schizophrenia in a Randomized, Open-label, Parallel-Arm, Pivotal Study.	The Journal of clinical psychiatry 2023; 84(5): p4889
	^a Harlin, M., et al. Safety and Tolerability of Aripiprazole 2-Month Ready-to- Use 960 mg in Adult Patients with Schizophrenia or Bipolar I Disorder.	CNS spectrums 2023; 28(2): 237-238.
	^a Harlin, M., et al. Pharmacokinetic Profile of Aripiprazole 2-Month Ready-to- Use 960 mg in Adult Patients with Schizophrenia or Bipolar I Disorder.	CNS spectrums 2023; 28(2): 256
	^a Madera-McDonough, J., et al. Safety and Efficacy of Aripiprazole 2-Month Ready-to- Use 960 mg in Adult Patients with Bipolar I Disorder.	CNS spectrums 2023; 28(2): 244
	^a Such, P., et al. Safety and Efficacy of Aripiprazole 2-Month Ready-to- Use 960 mg in Adult Patients with Schizophrenia.	CNS spectrums 2023; 28(2): 242-243

Source: Table 10, pp42-43 of the submission.

^a Conference abstracts; excluded due to limited data available.

- 6.6 The key features of the direct randomised trial are summarised in

6.7 Table 3.

Table 3: Key features of the included evidence

Trial	N	Design / duration	Intervention	Comparator	Bias	Patient population	Key Outcomes
Trial 031-201-00181	266 (Schizophrenia: 185; Bipolar-I disorder: 81)	P1b, MC, R, OL 32 weeks	A2M	AOM	Low ^a for PK outcomes; high ^b for other efficacy and safety outcomes	Schizophrenia or bipolar I disorder, aged 18-64y, BMI 18-35 kg/m ² , prior history of tolerating oral aripiprazole or AOM ^c	PK, safety and tolerability, PANSS, CGI-S/I and SWN-S

Source: Compiled during the evaluation based on Figure 7, p53 of the submission; Table 11, pp47-48 of the submission; Table 14, pp55-56 of the submission; Table 15, pp57-58 of the submission, Table 20, pp69-70 of the submission.

AOM = aripiprazole once monthly; BMI = Body mass index; CGI-S/I = Clinical Global Impression - Severity/Improvement; A2M = aripiprazole two-monthly; MC = multicentre; OL = open-label; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetics; p1b = phase 1b; R = randomised; SWN-S = Subjective Well-being under Neuroleptic treatment - Short Form; y = year.

a Objectively assessed PK outcome measures.

b Subjectively assessed secondary outcome measures, including PANSS, CGI-S/I, and SWN-S.

c Also on non-aripiprazole antipsychotics among participants enrolled on sparse sampling, which included less frequent PK blood sampling timepoints compared to robust sampling³.

- 6.8 Trial 031-201-00181 was at risk of several potential biases due to its open-label design (participants, investigators, and statisticians were not blinded to treatment assignments). There was a high risk of selection, performance and detection bias as participants and investigators were not blinded to the treatment allocation. However, any bias was more likely to affect subjective outcomes, such as Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression—Severity/Improvement (CGI-S/I) (clinician-reported) and Subjective Well-being under Neuroleptic Treatment-Short Form (SWN-S; patient-reported), rather than objective outcomes, such as PK parameters. During the evaluation, the overall risk of bias was assessed as low for the PK parameters and high for the subjective efficacy outcomes in Trial 031-201-00181.
- 6.9 Trial 031-201-00181 required participants to be stabilised on any one of a wide range of atypical antipsychotic medications, except clozapine, which was not permitted. Overall, only 4.3% of the participants with schizophrenia were stabilised on AOM prior to entering the trial. The remaining participants had to be previously treated with oral aripiprazole to establish tolerability.
- 6.10 Trial 031-201-00181 did not collect data relating to exacerbation or relapse rates, which have been used to support previous submissions for LAIs in schizophrenia.
- 6.11 The PK results were based on the whole trial sample that consisted of both schizophrenia and BP-I disorder participants. The submission noted that the PK profiles between the 2 arms should be similar, and the approach was deemed suitable for the analysis. The primary safety and secondary efficacy endpoints were based on the schizophrenia subpopulation only.

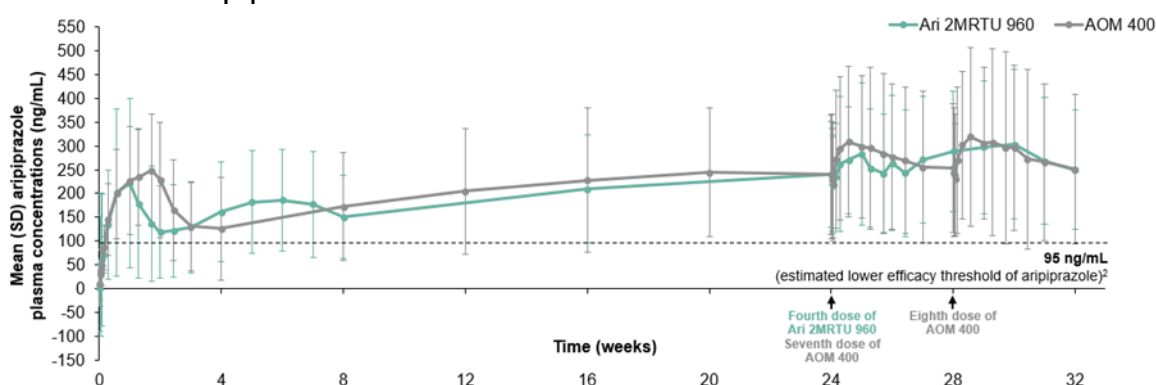
³ The PK parameters were sourced from a mix of robust (n= 84) and sparse (n= 182) samples in the trial, with the robust sampling schedule providing more frequent blood sampling time points for PK analyses (pp 43-44 of the submission). Most PK parameters were only collected for the robust sampling schedule.

- 6.12 The submission stated that there exists an extensive body of evidence supporting the use of AOM in the maintenance setting (based on evidence from the ASPIRE US and ASPIRE EU trials), therefore an “exposure-matching” or “PK bridging” development pathway was considered reasonable to demonstrate the established safety and efficacy of AOM to A2M. The TGA considered that a sufficient PK bridge was established (p54 of the TGA Clinical Evaluation Report for A2M).
- 6.13 The submission suggested a non-inferiority margin in terms of predicted minimum aripiprazole plasma concentration (C_{min}) of ≥ 95 ng/mL. The submission noted that a patient with schizophrenia and a predicted minimum aripiprazole plasma concentration (C_{min}) of ≥ 95 ng/mL was 4.41 times less likely to relapse compared with a person with a predicted C_{min} of < 95 ng/mL (Wang 2022). Trial 031-201-00181 did not specify a non-inferiority margin for any PK parameters. However, the trial was powered so that the lower bound of the 90% confidence interval (CI) of the geometric means ratio (GMR) of the following was greater than 80%:
- The plasma concentration of aripiprazole 56 days post-dose (C_{56}) and area under the concentration-time curve of aripiprazole from time zero to 56 days post-dose (AUC_{0-56}) after the 4th dose of A2M;
 - The plasma concentration of aripiprazole 28 days post-dose (C_{28}) and area under the concentration-time curve of aripiprazole from time zero to 28 days post-dose (AUC_{0-28}) after the 7th and 8th doses of AOM.
- 6.14 For the secondary outcome, the submission proposed a non-inferiority margin of a 7-point difference in the mean change from the baseline of the total PANSS score. This was consistent with the previously accepted claims of non-inferiority in schizophrenia of a 7-point difference in the total PANSS score (para. 8.4, paliperidone, Public Summary Document (PSD), November 2007 PBAC meeting; para. 9.2, lurasidone hydrochloride, PSD, March 2014 PBAC meeting; para. 6.10, brexpiprazole, PSD, March 2017 PBAC meeting; para. 6.9, cariprazine, PSD, November 2020 PBAC meeting).
- 6.15 The submission did not propose non-inferiority margins for CGI-S/I and SWN-S. The Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review Clinical Review Report for brexpiprazole, an atypical antipsychotic drug indicated for the treatment of schizophrenia in adults, recognised a non-inferiority margin for total CGI-S score of a one-point difference.
- 6.16 The trial was not powered for non-inferiority or to detect statistically significant differences between the treatment arms within the schizophrenia subpopulation for any secondary clinical outcomes, particularly the PANSS.

Comparative effectiveness

- 6.17 As noted above, the primary outcomes for Trial 031-201-00181 were pharmacokinetic outcomes. Figure 1 presents plasma concentration results following the 4th dose of A2M or the 7th and 8th dose of AOM over 32 weeks period.

Figure 1: Mean (SD) aripiprazole plasma concentration (ng/mL) after 4th dose of A2M vs 7th and 8th doses AOM over 32 weeks in the PK population in Trial 031-201-00181



Source: Figure 10, p80 of the submission

AOM = aripiprazole once-monthly; Ari 2MRTU = aripiprazole 2 month ready to use; A2M = Aripiprazole two-monthly; SD = standard deviation.

Note: Data for the first dose were for participants enrolled to the robust sampling schedule only (A2M 960 mg, n = 42 (Day 0–56); AOM 400 mg, n = 42 (Day 0–28)). Data for all other time points were for participants enrolled to the sparse (A2M 960 mg, n = 90; AOM 400 mg, n = 92) and robust (A2M 960 mg, n = 42; AOM 400 mg, n = 42) sampling schedules.

Note: Dotted line represented the estimated lower efficacy threshold of aripiprazole (95 ng/mL) (Wang 2022).

Note: The PK population included participants with schizophrenia or BP-I disorder.

6.18 The submission noted that aripiprazole A2M and AOM maintained mean aripiprazole plasma concentrations above the predetermined minimum efficacy threshold of ≥ 95 ng/mL throughout the 56-day as well as for the entire 32-week trial period (Figure 1).

6.19 The submission noted that the last (4th) dose of A2M compared with the sum of the 7th and 8th doses of AOM had:

- Similar aripiprazole plasma exposure over the respective 56-day (AUC_{0-56}) and 28-day (AUC_{0-28}) dosing intervals (GMR=1.006, 90% CI: 0.851, 1.190);
- Similar aripiprazole plasma concentrations following the last doses of A2M and AOM on the respective last day of the dosing intervals (C_{56}/C_{28}) (GMR=1.011, 90% CI: 0.893, 1.145);
- Similar maximum (peak) plasma aripiprazole concentration (C_{max}) following the last doses of A2M versus AOM (GMR=1.071, 90% CI: 0.903, 1.270);
- Higher median time to maximum peak PK (T_{max}) (28 days vs 4.1 days); and
- Higher mean peak-to-trough percent fluctuation (PTF) (63.4% vs 48.3%).

6.20 The submission noted that the lower limits of the 90% CI of the GMRs were greater than the pre-specified 0.80 threshold for the primary PK endpoints, demonstrating bioequivalence between A2M and AOM.

6.21 The TGA clinical evaluation report concluded that the PK parameters, in terms of concentrations and exposure, were similar between A2M and AOM. It noted the following: “In the pivotal PK Study 181, the similarities of aripiprazole concentrations and exposure were established between aripiprazole 2M LAI 960 mg and aripiprazole IM depot 400 mg, as the GMRs and 90% CIs for the primary PK endpoints (C_{56} following

the 4th dose of aripiprazole 2M LAI 960 mg versus C₂₈ following the 8th dose of aripiprazole IM depot 400 mg, and AUC₀₋₅₆ following the 4th dose of aripiprazole 2M LAI 960 mg versus the sum of AUC₀₋₂₈ following the 7th and 8th dose of aripiprazole IM depot 400 mg) were greater than 0.80” (p34 of the TGA clinical evaluation report for A2M).

6.22 Table 4 presents the clinical efficacy outcome results for the schizophrenia subpopulation in Trial 031-201-00181.

Table 4: Efficacy outcomes at Week 32 for the schizophrenia efficacy subpopulation (LOCF) – Trial 031-201-00181

Efficacy outcomes ^a	A2M		AOM		Mean difference (95%CI)
	n	Score, Mean (SD)	n	Score, Mean (SD)	
PANSS total score					
Baseline	92	62.2 (13.7)	93	61.6 (13.3)	-0.90 (-3.93, 2.13)
Week 32	89	59.6 (13.6)	85	59.9 (12.0)	
Change from baseline at week 32	89	-2.6 (11.7)	85	-1.7 (8.5)	
CGI-S score					
Baseline	92	3.3 (0.9)	93	3.1 (0.9)	-0.20 (-0.39, -0.01)
Week 32	89	3.0 (0.9)	85	3.0 (0.9)	
Change from baseline at week 32	89	-0.3 (0.6)	85	-0.1 (0.7)	
CGI-I score^b					
Week 8	83	3.8 (0.9)	81	3.5 (1.3)	NA
Week 32	88	3.5 (1.0)	82	3.6 (0.9)	
SWN-S total score					
Baseline	92	94.1 (14.8)	93	95.9 (16.6)	1.10 (-3.60, 5.80)
Week 32	89	94.4 (20.0)	84	95.2 (18.2)	
Change from baseline at week 32	89	0.3 (14.8)	84	-0.8 (16.6)	

Source: Tables 24-27, pp84-86, Figure 11, p84 of the submission. Text in Italics added during the evaluation.

AOM = aripiprazole once-monthly; A2M = aripiprazole two-monthly; CGI-S = Clinical Global Impression – Severity; CGI-I = Clinical Global Impression – Improvement; LOCF = last observation carried forward; NA = Not Available; PANSS = Positive and Negative Syndrome Scale; SWN-S = Subjective Well-being under Neuroleptic Treatment-Short Form.

^a Data for all efficacy outcomes were from the LOCF analysis (efficacy sample).

^b No baseline data were available for this outcome as the assessment of this scale began on Day 56 (Week 8).

Bold indicates statistically significant results.

Note: The mean difference for PANSS total score was verified during the evaluation using Revman.

6.23 The submission claimed that the treatment effects of A2M were comparable to AOM with respect to changes from baseline in the clinician-reported PANSS and CGI-S and the patient-reported SWN-S scale.

6.24 The lower bound of the 95% CI for mean difference of -3.93 points for the PANSS total score did not cross the 7-point non-inferiority margin. The submission stated that this supported the claim of non-inferior efficacy.

6.25 The change from baseline in the clinician-reported CGI-S score was statistically significantly lower in favour of A2M. However, the lower bound of the 95% CI of -0.39 points did not cross the one-point non-inferiority margin (paragraph 6.15 refers).

Comparative harms

6.26 Table 5 summarises the safety outcomes for the safety population in Trial 031-201-00181.

Table 5: Summary of key adverse events in Trial 031-201-00181

Event, n (%)	A2M (N=92)	AOM (N=93)	p value
TEAEs			
Any TEAE	61 (66.3)	59 (63.4)	0.7586
Serious/severe TEAE	5 (5.4)	5 (5.4)	1.0000
Discontinuation due to TEAE	3 (3.3)	7 (7.5)	0.3302
Death	1 (1.1)	0	1.0000
Incidence of TEAEs (≥5% of participants)			
Weight increase	20 (21.7)	17 (18.3)	0.5858
Injection site pain	14 (15.2)	9 (9.7)	0.2740
Insomnia	8 (8.7)	8 (8.6)	1.0000
Akathisia	8 (8.7)	7 (7.5)	0.7946
Anxiety	6 (6.5)	5 (5.4)	0.7668
Headache	6 (6.5)	2 (2.2)	0.1690
Constipation	4 (4.3)	5 (5.4)	1.0000
The overall incidence of TEAEs potentially related to study drug	73 (55.3)	61 (45.5)	0.1134
Any motoric TEAE	14 (15.2)	11 (11.8)	0.5265
Suicidality assessment	3 (3.3)	2 (2.2)	0.6823

Source: Tables 29-30, p89 of the submission; pp 89 & 92 of the submission. Text in Italics added during the evaluation.

AOM=aripiprazole once-monthly; A2M = aripiprazole two-monthly; TEAE = treatment-emergent adverse event.

TEAE defined as an AE that started after treatment; or if the event was continuous from baseline and was serious, treatment-related, or resulted in death, discontinuation, interruption, or reduction of the treatment. Multiple occurrences of a TEAE were counted once per MedDRA preferred term.

Note: P-values for between-arm comparisons were calculated using Fisher's exact test.

Note: All 185 randomised participants with schizophrenia received at least 1 study drug dose and were included in the safety analyses.

- 6.27 The incidence of any or serious treatment-emergent adverse events (TEAEs) were comparable in the A2M and AOM arms. The submission reported that the majority of TEAEs were mild to moderate in severity. There was one death due to cardiac arrest reported in the A2M arm, but it was judged to be unrelated to the study drug by the investigators.
- 6.28 The submission noted that the overall incidence of TEAEs that were considered by the investigators as potentially related to the study drug was slightly higher in the A2M (55.3%) arm versus the AOM (45.5%) arm.
- 6.29 The TEAEs considered by the investigators to be related to the study drug included injection site pain, akathisia events and weight increase. The submission stated that both injection site pain and weight increase were consistent with the known safety profile of aripiprazole, and the investigator considered none to be severe or serious. This was reasonable. Only akathisia was ultimately assessed to be related to the study drug. However, the incidence of akathisia was similar in both treatment arms (8.7% vs 7.5% for A2M and AOM, respectively).
- 6.30 The submission reported no significant differences in mean values or changes from baseline between the A2M and AOM treatment arms in the schizophrenia safety population for other safety outcomes⁴.

⁴ These outcomes include laboratory test results, vital signs, ECG parameters, and other safety variables.

- 6.31 The draft TGA PI for A2M noted that the most frequently observed TEAEs reported in patients with schizophrenia and BP-I disorder included weight increase (22.7%), injection site pain (18.2%), akathisia (9.8%), anxiety (8.3%), headache (7.6%), insomnia (7.6%), and constipation (6.1%) (p16 of draft TGA PI for A2M).

Benefits/harms

- 6.32 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.33 The submission claimed A2M was non-inferior in terms of effectiveness and safety compared with AOM.
- 6.34 The evaluation considered the therapeutic conclusion for effectiveness presented in the submission for A2M compared to AOM was supported by similar PK and secondary outcomes.
- 6.35 The evaluation considered the therapeutic conclusion for safety presented in the submission for A2M compared to AOM was adequately supported. The ESC noted a numerically higher proportion of patients experienced pain on injection with A2M compared to AOM.
- 6.36 The ESC considered that given the clinical claim was primarily informed by pharmacokinetic evidence comparing A2M to AOM, the conclusions of the TGA evaluation would be important to accept the claim of non-inferior comparative effectiveness. The Pre-PBAC Response (p2) reiterated the TGA CER concluded there were comparable treatment effects in terms of change in baseline for PANSS and CGI-S in patients with schizophrenia for AOM and A2M.
- 6.37 The PBAC considered that the claim of non-inferior comparative effectiveness safety was overall likely to be supported by the available data, and noted the advice of the TGA clinical evaluator and Delegate, given the primary outcome of the pivotal trial was based on pharmacokinetic parameters.

Economic analysis

- 6.38 The submission presented a CMA comparing A2M to AOM. This was appropriate given the claim of non-inferior efficacy and safety.
- 6.39 Table 6 describes key components and assumptions of the cost-minimisation approach.

Table 6: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on the trial evidence presented, effectiveness is assumed to be non-inferior to AOM.
Therapeutic claim: safety	Based on the trial evidence presented, safety is assumed to be non-inferior to AOM.
Evidence base	Direct randomised trial 031-201-00181 comparing A2M and AOM.
Equi-effective doses	<ul style="list-style-type: none"> • 1 A2M 960 mg injection every 56 days = 1 AOM 400 mg injection every 28 days • 1 A2M 720 mg injection every 56 days = 1 AOM 300 mg injection every 28 days
Direct medicine costs (AEMPs)	<ul style="list-style-type: none"> • A2M 960 mg = \$672.32; AOM 400 mg = \$630.92 • A2M 720 mg = \$546.12; AOM 300 mg = \$504.72
Other costs or cost offsets	Total administration costs over 56 days <ul style="list-style-type: none"> • A2M 960 mg = \$41.40; AOM 400 mg = \$82.80 • A2M 720 mg = \$41.40; AOM 300 mg = \$82.80

Source: Table 39, p109 and Table 40 p111 of the submission

AOM = aripiprazole once-monthly; A2M = aripiprazole two-monthly; LAI = long-acting injection.

- 6.40 The CMA was conducted over a period of 56 days.
- 6.41 The submission stated that the analysis duration had no price implications given that aripiprazole LAI is for maintenance treatment, and there was no loading dose requirement for A2M.
- 6.42 The submission included a cost offset for a single GP visit in the CMA. This was not consistent with the CMAs for AOM vs aripiprazole tablets or paliperidone LAI (para. 6.37, aripiprazole PSD, July 2014, PBAC meeting) or with the CMA of paliperidone 6-monthly vs 3-monthly, or 3-monthly versus 1-monthly (para. 6.25, paliperidone palmitate, PSD, March 2022 PBAC meeting). In the evaluation for paliperidone 3-monthly, the ESC noted that “contact between patient and health practitioner should be based on clinical need and not be based solely on the administration interval for medicines” and considered that “GP visits may include proper clinical management of schizophrenia, such as monitoring of glycated haemoglobin (HbA1c) and lipid levels while being treated with paliperidone” (para. 6.24 & 6.25, paliperidone PSD, November 2016 PBAC meeting). Consequently, GP visits for injection may not be avoided and claiming an offset for these may not be reasonable. The ESC noted ‘proper clinical management’ would also include management of other health concerns a person may have. The ESC also considered an uncertain proportion of antipsychotic LAI administration would also occur in non-GP/community care settings.
- 6.43 The Pre-Sub-Committee Response (PSCR) argued the inclusion of the administration cost is relevant because there would be some clinician visits for the purpose of AOM administration however accepted, for consistency with prior PBAC decision-making, to remove the GP cost offsets from the CMA and financial estimates. The ESC considered it was likely that few GP appointments would be solely for the purposes of AOM administration and therefore the removal of this offset was appropriate. The cost minimisation approach below has been updated from the submission base case to remove the GP consultation (i.e. based on drug acquisition cost only).
- 6.44 The equi-effective doses between aripiprazole A2M and AOM proposed by the submission are presented in Table 7.

Table 7: Proposed equi-effective doses for A2M and AOM

A2M every 56 days dose (mg)	AOM monthly equi-effective dose (mg)
A2M 720 mg injection every 56 days	AOM 300 mg injection every 28 days
A2M 960 mg injection every 56 days	AOM 400 mg injection every 28 days

Source: Table 40, p112 of the submission.

AOM = aripiprazole once-monthly; A2M = aripiprazole two-monthly.

6.45 Table 8 summarises the cost-minimisation of A2M and AOM.

Table 8: Results of the cost-minimisation approach

	AOM 400 mg	A2M 960 mg	AOM 300 mg	A2M 720 mg
Drug costs				
AEMP (list price)	\$315.46	\$630.92	\$252.36	\$504.72
Number of injections per 56 days	2	1	2	1
Drug acquisition	\$630.92	\$630.92	\$504.72	\$504.72

Source: Based on Table 43, p113 of the submission; Sheet 1, Workbook 3. Updated to remove GP cost offsets in the ESC advice.

AEMP = approved ex-manufacture price; AOM = aripiprazole once-monthly; A2M = aripiprazole two-monthly

Drug cost/patient/year

6.46 Table 9 summarises the estimated drug cost per patient per year for adults.

Table 9: Drug cost per patient for A2M

	A2M 960 mg	AOM 400 mg	A2M 720 mg	AOM 300 mg
Dose and frequency	960 mg every 8 weeks	400 mg every 4 weeks	720 mg every 8 weeks	300 mg every 4 weeks
Number of doses per year [A]	6.52 ^a	13.04 ^b	6.52 ^a	13.04 ^b
Drug cost per dose/ script (DPMQ ^c) [B]	\$720.28	\$364.13	\$577.79	\$292.90
Total cost/ patient/ year [C= A*B]	\$4,696.23	\$4,748.26	\$3,767.19	\$3,819.42

Source: Compiled during the evaluation with inputs sourced from Table 49, p117 of the submission, updated with revised A2M costs to remove GP cost offsets in the economic analysis

DPMQ = Dispensed Price for Maximum Quantity

^a 365.25/(8*7)

^b 365.25/(4*7)

^c Using markups valid at time of evaluation

6.47 At the proposed DPMQ prices, the estimated cost per patient per year of A2M 960 mg was \$4,696.23 and A2M 720 mg was \$3,767.19.

Estimated PBS usage & financial implications

6.48 This submission was not considered by DUSC. The submission used a market share approach. Table 10 outlines the key inputs relied on in the financial estimates.

Table 10: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value				Source	Comment
Market share						
Current scripts dispensed of AOM 300 and 400 mg	Year	300 mg	400 mg	AOM total	Service volumes available from the current PBS market.	This was reasonable and consistent with PBS market values.
	2015	2,139	10,825	12,964		
	2016	9,291	30,458	39,749		
	2017	15,526	42,438	57,964		
	2018	21,127	52,140	73,267		
	2019	26,347	62,339	88,686		
	2020	31,916	74,923	106,839		
	2021	35,320	80,747	116,067		
	2022	38,633	86,862	125,495		
2023	41,905	94,268	136,173			
Assumed annual growth rate in scripts for both AOM 300 mg and 400 mg	█ scripts per year				Assumed. The combined usage of AOM 300 mg and 400 mg post-COVID-19 increased, on average, █ each year.	This may be an underestimate. While the total AOM scripts increased by around █ per year post-COVID (2020-2023), the increase in scripts was significantly higher in the preceding years. Pre-COVID (between 2016 and 2020), the average growth was █ per year, while it was █ between 2017 and 2023.
Share of AOM 300mg and 400 mg based on the current trend	10224D (300 mg): 30% 10219W (400 mg): 70%				Service volumes available from the current PBS market. Assumed that 30%: 70% would also apply to A2M 720 mg and 960 mg doses, respectively.	This was reasonable and consistent with PBS data from 2018 to 2023. However, it was uncertain if the same ratio would apply for A2M 720 mg and 960 mg doses as participants in Trial 031-201-00181 did not require dose reductions. Further, it was uncertain whether these rates would remain constant over time.
Treatment utilisation						
Proportion of AOM scripts affected by A2M (substitution/uptake rate)	Yr 1: █ % Yr 2: █ % Yr 3: █ % Yr 4: █ % Yr 5: █ % Yr 6: █ %				Assumed to be similar to the substitution of paliperidone one-monthly by paliperidone 3-monthly	This was uncertain.
Adherence rate	Similar to AOM				Assumed.	This was reasonable.
Costs						
Proposed medicine (A2M 960 mg)	\$720.28				Proposed price (DPMQ)	Updated in ESC advice.
Proposed medicine (A2M 720 mg)	\$577.79				Proposed price (DPMQ)	Updated in ESC advice.

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Data	Value	Source	Comment
Comparator (AOM 400 mg)	\$364.13	DPMQ; PBS Item Number 10219W	This was verified.
Comparator (AOM 300 mg)	\$292.90	DPMQ; PBS Item Number 10224D	This was verified.
Patient co-payment for Year 2024	PBS: \$12.56; Share: 99.56% RPBS: \$6.54; Share: 0.44%	Average copayment calculated based on PBS item reports for AOM (items: 10224D and 10219W; January 2022 - December 2023). Calculated as the cross product of % share of PBS and RPBS services usages under different categories by their respective standard co-payments ^a .	This was reasonable.
MBS costs	\$41.40 per episode	MBS Item Number 23	Not appropriate to include costs for general practice consultations in financial estimates.

Source: Tables 44-45, p114 of the submission; Table 46, p115 of the submission; Table 47, p116 of the submission; Tables 48-50, p117 of the submission.

A2M = aripiprazole two-monthly; AOM = aripiprazole once-monthly; DPMQ = dispensed price for maximum quantify; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Co-payments for PBS services: general-ordinary services: \$31.60, General - Safety Net Services: \$7.70; Concessional - Ordinary Services: \$7.70; Concessional - Free Services: \$0.00; RPBS - Ordinary Services: \$7.70; RPBS - Safety Net Services: \$0.00

6.49 The submission assumed that each script of A2M was associated with a saving of one GP visit for injection. Assuming cost savings to the MBS due to reduced GP visits was not reasonable since any reduction in demand for a GP visit is likely to be otherwise utilised in the health system. As discussed in the economic analysis section, the PSCR accepted the removal of GP cost offsets from the economic analysis and financial estimates. The financial estimates have been updated to account for these changes in the ESC advice. Table 11 presents the estimated use and financial implications of listing A2M to the PBS/RPBS and its impact on the comparator AOM.

Table 11: Overall cost to Health Budget for listing A2M for schizophrenia

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	1	1	1	2	2	2
Estimated financial implications of A2M						
Net A2M costs to PBS/RPBS (excluding co-payments)	\$3	\$4	\$4	\$4	\$4	\$4
Substitution-related cost offsets						
Net substitution-related cost offsets, PBS/RPBS (excluding co-payments)	-\$3	-\$4	-\$4	-\$4	-\$4	-\$4
Net financial implications						
Net cost to PBS/RPBS	\$3	\$3	\$3	\$3	\$3	\$3

Source: Table 52, p118 of the submission; Table 54, p119 of the submission; Table 58, p121 of the submission. Updated in the ESC advice to reflect reduced A2M prices in the revised CMA and removal of MBS offsets.

A2M = aripiprazole two-monthly; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

¹ 10,000 to < 20,000

² 20,000 to < 30,000

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

- 6.50 The net financial impact of listing A2M for schizophrenia on the health budget over the first 6 years, updated for changes accepted in the PSCR to remove GP cost offsets from the CMA and financials was estimated to be a cost of \$0 to < \$10 million in Year 1, increasing to a cost of \$0 to < \$10 million in Year 6. The estimated total cost to the health budget was approximately \$0 to < \$10 million over 6 years. The small net cost is primarily driven by fewer co-payments associated with A2M compared to AOM.
- 6.51 The submission assumed that only AOM for schizophrenia (300 mg and 400 mg) would be the product replaced in practice by A2M for schizophrenia.
- 6.52 The submission assumed that % of patients on AOM would switch to A2M in Year 1, increasing to % in Year 6. The uptake of A2M was expected to be gradual and follow a similar trajectory to paliperidone 3-monthly away from paliperidone when paliperidone 3-monthly was first listed on the PBS in January 2019. This was uncertain.
- 6.53 The submission estimated that the AOM market would increase at a constant rate of 10,000 to < 20,000 scripts per year. This may be an underestimate. While the total AOM scripts increased by around 10,000 to < 20,000 per year post-COVID (2020-2023), the increase in scripts was significantly higher in the preceding years. Pre-COVID (between 2016 and 2020), the average growth was 10,000 to < 20,000 per year.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the General Schedule, Authority Required (STREAMLINED) listing of aripiprazole once per 2-month injection (A2M) for the maintenance treatment of schizophrenia in patients who are stabilised on the once-monthly injectable form of aripiprazole (AOM). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost effectiveness of A2M would be acceptable if it were cost minimised to AOM.
- 7.2 The PBAC advised the equi-effective doses were:
- 1 injection of A2M 960 mg every 56 days = 2 injections of AOM 400 mg (given at 28-day intervals); and
 - 1 injection of A2M 720 mg every 56 days = 2 injections of AOM 300 mg (given at 28-day intervals).
- 7.3 The PBAC considered the requested listing was reasonable and consistent with the listing of AOM, which includes provision for nurse practitioner prescribing. The PBAC also considered the additional standard notes regarding no increases to maximum quantities and repeats, as well as a note regarding the need for patients to be stable on AOM prior to moving to A2M, were appropriate. The Committee noted that between consideration by the ESC in June 2024 and consideration in December 2024 the existing listings of aripiprazole had been updated to remove the Shared Care model administrative advice and such a note was not required.
- 7.4 The PBAC considered there was a clinical place for this longer acting formulation of aripiprazole, as some patients with schizophrenia have low engagement with the health system and compliance may be simpler to maintain with fewer injections.
- 7.5 The PBAC considered the nominated comparator of AOM was reasonable, as the requested listing requires patients to be stable on AOM before moving to the A2M formulation.
- 7.6 The PBAC noted the submission was supported by one open-label randomised controlled trial (RCT) comparing A2M to AOM in adults with schizophrenia (n=185) or bipolar-1 disorder (n=81) (Trial 031-201-00181), and that the primary outcomes were pharmacokinetic (PK) in nature, with secondary clinical outcomes including PANSS and CGI severity/improvement, safety and tolerability.
- 7.7 The PBAC noted the TGA Delegate considered the primary PK outcomes supported similarity between A2M and AOM being established (TGA Delegate's Overview). The PBAC noted that in terms of secondary clinical outcomes, the results for PANSS total score were not statistically significantly different and marginally statistically significantly in favour of A2M for CGI-S score (Table 4). The Committee acknowledged that as secondary outcomes, the trial was not powered to formally assess non-inferiority, however considered the results did not suggest any clinically significant

differences between A2M and AOM. The PBAC considered the claim of non-inferior comparative effectiveness of A2M and AOM was adequately supported.

- 7.8 In terms of comparative safety, the PBAC noted rates of treatment-emergent adverse events (TEAEs) and serious TEAEs were comparable for A2M and AOM. The PBAC noted other TEAEs such as weight increase, insomnia and akathisia events were consistent with the known safety profile of injectable aripiprazole and event rates were similar in the A2M and AOM arms. The PBAC noted injection site pain occurred in 15.2% of patients in the A2M arm compared to 9.7% of patients in the AOM arm and considered this was likely related to the larger injection volume. The PBAC considered the adverse event profiles of A2M and AOM were likely to be similar and the claim of non-inferior comparative safety was adequately supported.
- 7.9 The PBAC noted the submission presented a cost minimisation approach (CMA) based on drug acquisition costs and an offset for general practitioner (GP) attendances as the administration regimen for A2M was half that of AOM. The Committee agreed with the ESC it was unlikely those GP attendance reductions would be realised in practice (paragraph 6.42) and acknowledged the Sponsor had agreed to a revised CMA based on drug costs only in the PSCR and considered this was reasonable.
- 7.10 The PBAC noted the utilisation and financial estimates proposed a small net cost to the PBS of approximately \$0 to < \$10 million over 6 years and further noted this was largely driven by fewer patient co-payments as A2M requires less scripts.
- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because A2M is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over AOM, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met.
- 7.12 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 item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ARIPIPRAZOLE					
aripiprazole 960 mg/3.2 mL modified release injection, 3.2 mL syringe	NEW	1	1	2	Abilify Asimtufii
aripiprazole 720 mg/2.4 mL modified release injection, 2.4 mL syringe	NEW	1	1	2	Abilify Asimtufii
Category / Program: <input checked="" type="checkbox"/> GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new/existing code]					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: Patient dosage is to be determined as per the Therapeutic Goods Administration (TGA) approved Product Information.					
Indication: Schizophrenia					
Clinical criteria: Patient must have previously received and be stabilised on PBS-subsidised aripiprazole once-monthly injection					

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Lundbeck Australia welcomes the PBAC's positive recommendation of Abilify Asimtufii, an additional long acting every 2 months treatment option for Australians with schizophrenia. Reimbursed access to effective treatments is important for patients with schizophrenia who face a high burden of disease.