

**5.01 BREXPIRAZOLE,  
Oral tablet (1 mg, 2 mg, 3 mg, 4 mg) Rexulti<sup>®</sup>,  
Lundbeck Australia Pty Ltd.**

**1 Purpose of Application**

1.1 Authority Required (STREAMLINED) listing for brexpiprazole for the treatment of schizophrenia.

**2 Requested listing**

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

Name, Restriction, Manner of administration and form	Max. Qty	Nº. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
BREXPIRAZOLE Tablet 1 mg, 30	1	0	\$ [REDACTED]		
BREXPIRAZOLE Tablet 2 mg, 30	1	5	\$ [REDACTED]		
BREXPIRAZOLE Tablet 3 mg, 30	1	5	\$ [REDACTED]	Rexulti	Lundbeck Australia Pty Ltd
BREXPIRAZOLE Tablet 4 mg, 30	1	5	\$ [REDACTED]		

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Schizophrenia
<b>Restriction Level / Method:</b>	<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
<b>Administrative Advice</b>	<i>Shared Care Model</i> <i>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.</i>

2.2 Listing was sought on a cost-minimisation basis with aripiprazole or lurasidone (sponsor pre-PBAC response).

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

### **3 Background**

- 3.1 Brexpiprazole was not TGA registered at the time of PBAC consideration. The submission was made under TGA/PBAC Parallel Process. At the time of the ESC consideration, the Clinical Evaluation Report (Round 2) was available. At the time of PBAC consideration, the TGA Delegate's Overview was available.
- 3.2 Brexpiprazole has not been considered by PBAC previously.

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

### **4 Clinical place for the proposed therapy**

- 4.1 Schizophrenia occurs when a patient suffers from delusional beliefs, hallucinations, disorganised thinking and speech, cognitive impairment, abnormal motor behaviour and negative symptoms.
- 4.2 Brexpiprazole provides an alternative treatment to the currently listed atypical oral antipsychotics.

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

### **5 Comparator**

- 5.1 The submission nominated the main comparator as aripiprazole (oral tablets). The submission based its choice of the primary comparator on the mode of administration of the drug (oral tablet), class of the drug and the mechanism of action. The ESC noted brexpiprazole, like aripiprazole, is a partial D2 agonist. There are no other partial D2 agonists listed on the PBS for schizophrenia.
- 5.2 The submission nominated lurasidone (oral tablets) as a secondary comparator. The ESC noted the mechanism of action of lurasidone is different to that of brexpiprazole.
- 5.3 The ESC noted that the choice of comparators was critical as there are a number of other antipsychotics available on the PBS that may also be considered alternative therapies. For the requested population, the PBS-listed medicines olanzapine, paliperidone and ziprasidone were considered therapeutically equivalent and cost minimised to aripiprazole and lurasidone. Therefore, olanzapine, paliperidone and ziprasidone may also be comparators. The equi-effective doses and approximate monthly costs for olanzapine, paliperidone, ziprasidone, aripiprazole and lurasidone are presented in Table 1.
- 5.4 In the pre-PBAC response the sponsor argued that any comparison of older antipsychotics to brexpiprazole would be associated with significant uncertainties, including lack of exchangeability of trials due to differences in dates of the studies, and no scope for comparison in the maintenance treatment setting.
- 5.5 The submission also estimated that 10% of brexpiprazole use will occur in patients currently treated with asenapine. Risperidone, amisulpride, asenapine and quetiapine were considered therapeutically equivalent and cost minimised to each other. Therefore risperidone, amisulpride, asenapine and quetiapine may also be appropriate comparators.

- 5.6 The ESC noted the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders recommend amisulpride, aripiprazole, quetiapine, and ziprasidone as first line treatments for schizophrenia and olanzapine as a second line treatment (Figure 1, Australian and New Zealand Journal of Psychiatry 2016, Vol. 50(5) 1-117). However in Section E of the submission, the sponsor estimated that 10% of brexpiprazole use will occur in patients currently receiving olanzapine.
- 5.7 The Pre-Sub-Committee Response (PSCR) noted that lurasidone, the most recent antipsychotic to be PBS listed, was listed on a cost-minimisation basis with its pharmacological analogue ziprasidone. Regarding the clinical use of lurasidone, the PBAC considered that it 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 (lurasidone PSD, March 2015).
- 5.8 In the pre-PBAC response the sponsor argued that the appropriate main comparator for brexpiprazole was aripiprazole. The sponsor argued aripiprazole, like brexpiprazole, is a partial D2 agonist and therefore a pharmacological analogue of brexpiprazole. However, the sponsor conceded that lurasidone was also an acceptable comparator.
- 5.9 The PBAC recalled that the medicines olanzapine, paliperidone, ziprasidone, aripiprazole and lurasidone had all been recommended for listing on the basis that they delivered similar effectiveness and safety in the treatment of schizophrenia. Olanzapine, the first of the medicines in this group to be listed, was recommended for listing on a cost-effectiveness basis compared to risperidone and risperidone, amisulpride, asenapine and quetiapine were all recommended for listing on a cost-minimisation basis to each other as they all delivered similar effectiveness and safety.
- 5.10 The PBAC accepted that the relevant comparator should come from the group of medicines that were listed on a cost-minimisation basis compared to olanzapine (olanzapine, paliperidone, ziprasidone, aripiprazole and lurasidone) on the basis that, on balance, brexpiprazole has been shown to be non-inferior to lurasidone (see under Clinical Claim). The PBAC noted that it could only recommend listing brexpiprazole at a higher price than an alternative therapy or therapies if it is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. However, the PBAC was satisfied that olanzapine, the lowest cost medicine in the group of potential alternatives, should not be considered an alternative therapy as it is now recognised to have an inferior safety profile compared to the other medicines in the group. The PBAC noted of the four remaining medicines in this group, lurasidone has the lowest cost based on equi-effective doses (see Table 1). The PBAC considered lurasidone to be the appropriate comparator.

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**Table 1: Price comparison of anti-psychotics**

Drug	Brexpiprazole	Lurasidone	Ziprasidone	Aripiprazole	Paliperidone	Olanzapine	Risperidone
ATC Group	N05AX	N05AE	N05AE	N05AX	N05AX	N05AH	N05AX
PBS Listing	Authority Required (STREAMLINED) - Schizophrenia	Authority Required (STREAMLINED) - Schizophrenia (4246)	Authority Required (STREAMLINED) - Schizophrenia (4246)	Authority Required (STREAMLINED) - Schizophrenia (4246)	Authority Required (STREAMLINED) - Schizophrenia (4246)	Authority Required (STREAMLINED) - Schizophrenia (4304 and 5856)	Authority Required (STREAMLINED) - Schizophrenia (5903 and 4246)
Formulary	F1	F1	F2	F2	F1	F2	F2
Basis of recommendation	Seeking cost minimisation compared to aripiprazole.	Cost minimised to ziprasidone.	Cost minimised to olanzapine.	Cost minimised to olanzapine.	Cost minimised to olanzapine.	Acceptable cost-effectiveness compared to risperidone.	
Equi-effective dose per Therapeutic Relativity Sheets, vs olanzapine	Indirect: 4.19mg <sup>a</sup>	Indirect: 88mg <sup>b</sup>	125.75mg	21.3mg	11.4 mg <sup>#</sup>	15.032mg	NA
Ex-man 1 Feb 2017	Requested: \$ [REDACTED] per 1mg, 2mg, 3mg, 4mg, 30	AEMP = \$123.94 per 80mg, 30	AEMP = \$150.11 per 60mg, 60	AEMP = \$169.97 per 20mg, 30	AEMP = \$178.12 per 9mg, 28	AEMP = \$20.34 per 15mg, 28	AEMP = \$16.52 for 2mg, 60
Price (AEMP) for equi-effective dose for 30 days (equivalent to olanzapine 15.032mg)	Requested: based on aripiprazole price (comparison vs lurasidone also presented)	\$136.33	\$157.30	\$181.02	\$241.73	\$21.84	NA

Source: Compiled by Department of Health based on advice from the ESC meeting

AEMP = Approved Ex-Manufacturer Price

a Based on equi-effective doses of 3.58mg brexpiprazole and 18.20mg aripiprazole

b Based on equi-effective doses of 80mg lurasidone and 114.15mg ziprasidone

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

6.1 There was no hearing for this item.

### ***Consumer comments***

6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The PBAC specifically noted the advice from Schizophrenia Fellowship of NSW that the use of brexpiprazole may reduce the rate of metabolic syndrome and the induction of type 2 diabetes in patients, compared with treatment with other PBS listed antipsychotics. The PBAC also noted the previous advice from Royal Australian and New Zealand College of Psychiatrists (RANZCP) along with that of the Schizophrenia Fellowship of NSW that there was a clinical need for a broad range of medicine to treat mental illnesses.

### ***Clinical trials***

6.3 The submission is based on:

- one head-to-head randomised open-label trial comparing brexpiprazole tablets with aripiprazole tablets in the acute setting: 331-137-008 (N = 97). This trial formed the basis of the cost-minimisation of brexpiprazole with aripiprazole.
- one multi-arm randomised trial comparing four arms of different brexpiprazole tablets with aripiprazole and placebo in the acute setting: 331-07-203 (N = 459). Although this trial was used to provide a direct comparison of brexpiprazole with aripiprazole, it was not used in the cost-minimisation of brexpiprazole with aripiprazole. As this trial was a fixed-dose, dose finding study this is reasonable.
- an indirect comparison of brexpiprazole and aripiprazole in the acute setting using placebo as a common comparator. This is based on five brexpiprazole trials (331-10-002, 331-20-230, 331-10-231, 331-07-203, 14644A) and seven aripiprazole trials (31-93-202, 31-94-202, Kane (2002), Potkin (2003), Cutler (2006) McEvoy (2007), Durgam (2015)).
- an indirect comparison of brexpiprazole and lurasidone in the acute setting using placebo as a common comparator. This is based on five brexpiprazole trials (as above) and seven lurasidone trials (Loebel (2013), Loebel (2016), Melzel (2011), Nakamura (2009), Nasrallah (2013), Ogasa (2013), and Potkin (2015)).
- an indirect comparison of brexpiprazole and lurasidone in the maintenance setting using placebo as a common comparator. This is based on the 331-10-232 brexpiprazole trial and Tandon (2016) lurasidone trial.

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

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**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials, brexpiprazole vs. aripiprazole		
331-07-203 (NCT00905307 CTRI/2009/091/000952 EUCTR2009-012567-33-BG EUCTR2009-012567-33-SK)	Clinical Study Report. A phase 2, 6-week, multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of oral OPC-34712 once daily and aripiprazole once daily for the treatment of hospitalised adult patients with acute schizophrenia.	9 March 2011.
331-13-008 (NCT02054702)	Clinical Study Report. An exploratory, multicentre, open-label, flexible-dose brexpiprazole (OPC-34712) trial in adults with acute schizophrenia.  Citrome L, Ota A, Nagamizu K, Perry P, Weiller E, Baker RA. The effect of brexpiprazole (OPC-34712) and aripiprazole in adult patients with acute schizophrenia: results from a randomised, exploratory study.  Citrome L, Ota A, Nagamizu K, Perry P, Weiller E, Baker R. The effect of brexpiprazole (OPC-34712) versus aripiprazole in adult patients with acute schizophrenia: an exploratory study.	18 February 2015.  <i>Int Clin Psychopharmacology</i> 2016; 31(4); 192-201.  <i>Biol Psychiatry</i> 2015; 77: 203S.
Supplementary randomised trials, Brexpiprazole (acute treatment settings)		
331-10-002 (NCT01451164 JPRN-JapicCTI-111631)	CSR A dose-finding trial of OPC-34712 in patients with schizophrenia.	Ongoing. Report 24 November 2015.
331-10-230 (NCT01393613 EUCTR2011-002513-11-SK)	CSR A phase 3, multicentre, randomised, double-blind, placebo-controlled trial of fixed-dose OPC-34712 (4, 2, and 1 mg/day) in the treatment of adults with acute schizophrenia.  Kane JM, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, Nyilas M, Carson WH, Sanchez R, Eriksson H. A multicentre, randomised, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia.  Kane, J., A. Skuban, J. Youakim, J. Ouyang, M. Hobart, S. Pfister, S. Offord, R. McQuade, M. Nyilas, W. Carson, R. Sanchez (2014) A multicenter, randomized, controlled, phase III trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia.	February 2014  <i>Schizophrenia Res</i> 2015; 164: 127-135.  <i>Neuropsychopharmacology</i> 39, S357-s358
331-10-231 (NCT01396421 EUCTR2011-002538-38-LV)	CSR A phase 3, multicentre, randomised, double-blind, placebo-controlled trial of three fixed doses of OPC-34712 in the treatment of adults with acute schizophrenia.  Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, Nyilas M, Carson WH, Sanchez R, Eriksson H. Efficacy and safety of brexpiprazole for the	January 2014  <i>Am J Psychiatry</i> 2015; 172: 870-880.

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	treatment of acute schizophrenia: a 6-week randomised, double-blind, placebo-controlled trial.  Correll, C., A. Skuban, J. Youakim, J. Ouyang, M. Hobart, S. Pfister, R. McQuade, M. Nyilas, W. Carson and R. Sanchez (2014) "Brexiprazole for the treatment of acute schizophrenia: A randomized, controlled trial."	<i>Neuropsychopharmacology</i> 39, S474
14644A (NCT01810380 EUCTR2012-002252-17-RO EUCTR2012-002252-17-DE)	CSR Interventional, randomised, double-blind, parallel-group, placebo-controlled, active-reference, flexible-dose study of brexpiprazole in patients with acute schizophrenia.	December 2014
Brexiprazole, maintenance treatment setting		
331-10-232 (NCT01668797 EUCTR2011-005766-38-RO)	CSR A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) as Maintenance Treatment in Adults With Schizophrenia	February 2015
Aripiprazole trials, acute treatment settings		
Study 31-93-202	CSR 31-93-202, efficacy and tolerability of ascending doses of OPC-14597 compared to placebo and to haloperidol in acutely relapsing hospitalized schizophrenic patients.	-
Study 31-94-202	CSR A dose ranging study of the efficacy and tolerability of OPC-14597 in acutely relapsing hospitalized schizophrenic patients.	-
Study 331-07-203 (NCT00905307 CTRI/2009/091/000952 EUCTR2009-012567-33-BG EUCTR2009-012567-33-SK)	CSR A phase 2, 6-week, multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of oral OPC-34712 once daily and aripiprazole once daily for the treatment of hospitalised adult patients with acute schizophrenia	-
Kane (2002)	Kane JM, Carson WH, Saha AR, Mc Quade RD, Ingenito GG, Zimbroff DL, Ali MW. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder.	<i>J Clin Psychiatry</i> 2002; 63: 763-771.
Potkin (2003)	Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, Stringfellow J, Ingenito G, Marder SR. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder.	<i>Arch Gen Psychiatry</i> 2003; 60: 681-690.
Cutler (2006) (NCT00080327)	Cutler AJ, Marcus RN, Hardy SA, O'Donnell A, Carson WH, Mc Quade RD. The efficacy and safety of lower doses of aripiprazole for the treatment of patients with acute exacerbation of schizophrenia.	<i>CNS Spectrums</i> 2006; 11 (9): 691-702.
Durgam (2015) (NCT01104766)	Durgam S, Cutler AJ, Lu K, Migliore R, Ruth A, Laszlovszky I, Nemeth G, Meltzer HY. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomised, double-blind, placebo- and active-controlled trial.	<i>J Clin Psychiatry</i> 2015; 76 (12): 1574-82.
Aripiprazole trials, maintenance treatment settings		
Pigott (2003)	Pigott TA, Carson WH, Saha AR, Torbeyns AF, Stock	<i>Journal of Clinical</i>

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	EG, Ingenito GG. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study.	<i>Psychiatry</i> 2003; 64: 1048-56.
Lurasidone trials, acute treatment settings		
Study D1050233 (NCT00790192 ISRCTN64695913)	Loebel A, Siu CO, Cucchiaro JB, Pikalov AA, Harvey P. Daytime sleepiness associated with lurasidone and quetiapine XR: results from a randomized double-blind, placebo-controlled trial in patients with schizophrenia.  Loebel A, Cucchiaro J, Sama K, Xu L, Hsu C, Kalali AH, Pikalov A, Potkin SG. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial.  Harvey PD, Siu CO, Hsu J, Cucchiaro J, Maruff P, Loebel A. Effect of lurasidone on neurocognitive performance in patients with schizophrenia: a short-term placebo- and active-controlled study followed by a 6-month double-blind extension.	<i>CNS Spectrums</i> 2014; 19 (2): 197-205.  <i>Schizophrenia Res</i> 2013; 145: 101-9.  <i>Eur Neuropsychopharmacol</i> 2013; 23: 1373-1382
Study D1050231 (NCT00615433 ISRCTN33909010)	Melzer HY, Cucchiaro J, Silva R, Ogasa M, Phillips D, Xu J, Kalali A, Schweizer E, Pikalov A, Loebel A. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study.	<i>Am J Psychiatry</i> 2011; 168: 957-67.
Study D1050049 (NCT00044044)	Potkin SG, Kimura T, Guarino J. A 6-week, double-blind, placebo-and haloperidol-controlled, phase II study of lurasidone in patients with acute schizophrenia. <i>Ther Adv Psychopharmacology</i> 2015; 5 (6): 322-331. 2015). "Corrigendum."	<i>Ther Adv Psychopharmacol</i> 5(6): 369.
Study D1050303 (NCT01821378 EUCTR2012-005271-14-SK)	Loebel A, Silva R, Goldman R, Watabe K, Cucchiaro J, Citrome L, Kane JM. Lurasidone dose escalation in early nonresponding patients with schizophrenia: a randomized, placebo-controlled study.	<i>J Clin Psychiatry</i> 2016;
Study D1050196 (NCT00088634)	Nakamura M, Ogasa M, Guarino J, Phillips D, Severs J, Cucchiaro J, Loebel A. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial.	<i>J Clin Psychiatry</i> 2009; 70 (6): 829-36.
	Ogasa M, Kimura T, Nakamura M, Guarino J. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study.	<i>Psychopharmacology</i> 2013; 225: 519-30.
Lurasidone trials, maintenance treatment settings		
Study D1050238 (NCT01435928 EUCTR2011-001711-31-SK)	Tandon R, Cucchiaro J, Phillips D, Hernandez D, Mao Y, Pikalov A, Loebel A. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia.	<i>J Psychopharmacology</i> 2016; 30 (1):69-77.

Source: compiled during evaluation.

6.5 Direct comparison: brexpiprazole versus aripiprazole (acute setting). The key features of the direct randomised trials are summarised in the table below.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>brexpiprazole vs. aripiprazole</b>					
331-13-008	97	R, OL, MC 6 weeks	High	schizophrenia	PANSS total score, CGI-S, PANSS positive and negative sub-scores, CGI-I
331-07-203	459 <sup>a</sup>	R, DB, MC 6 weeks	Low	schizophrenia	PANSS total score, CGI-S, PANSS positive and negative sub-scores, CGI-I

Abbreviations: DB=double blind; MC=multi-centre; OL=open label; R=randomised, na= not applicable. Note: a = of the six arms only three were presented in the submission (brexpiprazole 2.5 mg ± 0.5 mg (n = 90), aripiprazole (n = 50) and placebo (n =95)). Source: compiled during the evaluation

- 6.6 Neither trials 331-13-008 nor 331-07-203 were designed to compare brexpiprazole with aripiprazole; the analyses were performed post-hoc.
- 6.7 The ESC noted that trial 331-13-008 was an open-label exploratory study with a subjective outcome measure potentially resulting in a high risk of bias, and trial 331-07-203 was a dose finding study. The ESC further noted 37% of patients discontinued treatment in 331-13-008.

### **Comparative effectiveness**

#### **Direct comparison: brexpiprazole versus aripiprazole (acute setting)**

- 6.8 The primary outcome assessed was a PANSS total score which consists of 3 subscales containing a total 30 symptom constructs, each ranked on a 7-point severity scale.
- 6.9 The results are presented in Table 4 below. The analysis of the primary outcome (PANSS total score) indicate no statistically significant differences in the comparison of brexpiprazole to aripiprazole in the acute setting. There was one statistically significantly different secondary outcome in the PANSS negative score that favoured brexpiprazole (Trial 331-137-008). The submission stated that this result was unlikely to be clinically relevant. This is reasonable.
- 6.10 The PBAC has previously accepted that the minimally clinical important difference (MCID) for the PANSS total score is seven (7) points (paliperidone PSD, November 2007). A MCID of 7 was also used for the March 2015 lurasidone submission (lurasidone PSD, March 2015). The PSCR notes that there is no consensus and established MCID for PANSS total score in the literature. The ESC considered use of a MCID of 7 points provided consistency with previous PBAC submissions.
- 6.11 The submission claimed non-inferiority of brexpiprazole compared to aripiprazole in the acute setting. The 95% CI for the PANSS total score in trial 331-07-203 included the MCID of seven points; and is in favour of aripiprazole. This result does not support a claim of non-inferiority. Based on the results of the 331-13-008 trial the claim of non-inferiority may be supported as the mean difference in the PANSS total score was not statistically significant and the upper limit of the 95% CI did not reach seven points. However 331-13-008 was a small open label trial with a 37% discontinuation rate.

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- 6.12 The PSCR argued the upper confidence limit for the mean difference for PANSS total score in 331-07-203 exceeds the stated MCID of 7 by only 1.83 points on the 210-point scale.
- 6.13 The PSCR presented the results of a meta-analysis of 331-07-203 and 331-13-008. The PSCR noted that the submission did not include this meta-analysis because of differences in the trial design and their statistical analyses (331-07-203 was double-blind, the primary analysis was last observation carried forward (LOCF); 331-13-008 was open-label, the primary analysis was mixed effect model repeat measurement (MMRM)). The PSCR argued the meta-analysis supports the claim of non-inferiority with the weighted mean difference [95% CI] in baseline to endpoint change in PANSS total score of -0.98 [-5.84, 3.88].
- 6.14 Overall, the ESC considered the claim of non-inferiority of brexpiprazole and aripiprazole in the acute setting to be inadequately supported as the MCID was exceeded in study 331-07-203 and study 331-13-008 was potentially subject to bias given its open-label design.

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**Table 4: Results of patient-relevant outcome across the direct randomised trials**

Trial ID	n/N (%)	Brexpiprazole Mean (SD) Difference from baseline	n/N (%)	Aripiprazole Mean (SD) difference from baseline	Mean difference [95%CI]	p-value
<b>Primary Outcome: PANSS Total score</b>						
331-07-203 (LOCF)	90/90 (100%)	-16.19 (18.55)	50/50 (100%)	-17.98 (21.32)	1.79 [-5.25; 8.83]	0.62
331-13-008 (MMRM)	44/64 (69%)	-22.7 (12.1)	21/33 (64%)	-19.5 (12.0)	-3.20 [-9.45; 3.05]	0.32
<b>PANSS positive score</b>						
331-07-203 (LOCF)	90 (100%)	-4.94 (6.17)	50 (100%)	-6.60 (7.16)	1.66 [-0.70; 4.02]	0.17
331-13-008 (MMRM)	44/64 (69%)	-6.7 (4.0)	21/33 (64%)	-6.2 (3.8)	-0.50 [-2.51; 1.51]	0.63
<b>PANSS negative score</b>						
331-07-203 (LOCF)	90 (100%)	-3.84 (5.09)	50 (100%)	-3.00 (5.74)	-0.84 [-2.75; 1.07]	0.39
331-13-008 (MMRM)	44/64 (69%)	-4.5 (3.3)	21/33 (64%)	-2.8 (3.2)	-1.70 [-3.38; -0.02]	0.05
<b>CGI-S</b>						
331-07-203 (LOCF)	90 (100%)	-0.87 (1.11)	50 (100%)	-1.00 (1.21)	0.13 [-0.28; 0.54]	0.53
331-13-008 (MMRM)	44/64 (69%)	-1.6 (0.9)	21/33 (64%)	-1.3 (0.8)	-0.30 [-0.74; 0.14]	0.18
<b>Personal and Social Performance Scale (PSP)</b>						
331-07-203 (LOCF)	84/90 (93%)	10.67 (15.21)	50 (100%)	10.66 (13.13)	0.01 [-4.87; 4.89]	1.00
<b>Specific Levels of Functioning Total Scale Score</b>						
331-13-008 (LOCF)	50/64 (78%)	7.7 (14.8)	25/33 (76%)	5.5 (11.3)	-0.30 [-0.74; 0.14]	0.48
<b>Barratt Impulsiveness Scale 11-Item (BIS-11)</b>						
331-13-008 (LOCF)	49/64 (77%)	-2.7 (10.0)	25/33 (76%)	0.1 (6.9)	-2.80 [-6.69; 1.09]	0.16
<b>Response rate at week 6 (LOCF)</b>						
	n/N (%)	Brexpiprazole n (%)	n/N (%)	Aripiprazole n (%)	RR/RD/OR [95% CI]	p-value
331-07-203	90/90 (100%)	42 (46.7%)	50/50 (100%)	30 (60.0%)	RR: 0.78 [0.57; 1.07]	0.12
					RD: -0.13 [-0.30; 0.04]	0.13
					OR: 0.58 [0.29; 1.18]	0.13
331-13-008	64/64 (100%)	39 (60.9%)	33/33 (100%)	16 (48.5%)	RR: 1.26 [0.84; 1.88]	0.27
					RD: 0.12 [-0.08; 0.33]	0.24
					OR: 1.66 [0.71; 3.87]	0.24

Source: Table B.6.1, of the commentary.

Abbreviations: PANSS, positive and negative syndrome scale score; PSP, personal and social performance score; CGI-S, clinical global impression- severity of illness; CGI-I, clinical global impression, improvement; LOCF, last observation carried forward; ANCOVA, analysis of covariance; OC, observed cases; SLOF, specific levels of functioning; BIS-11, Barratt impulsiveness scale 11-item; MRMM, mixed model for repeated measures; CI, confidence interval; SD, standard deviation; RR = risk ratio; RD = risk difference; OR = odds ratio.

**Indirect comparison: brexpiprazole versus aripiprazole (acute setting)**

- 6.15 The results of the indirect comparison between brexpiprazole and aripiprazole in the acute setting in terms of the PANSS total score were statistically significant in favour of aripiprazole 4.31 (95%CI: 1.351; 7.269,  $p = 0.004$ ). Although the mean difference in the outcomes did not reach the MCID, the upper limit of the 95% CI for the differences between the two treatment groups was above 7 points in the LOCF analysis, which indicates that a difference in favour of aripiprazole cannot be excluded. Non-inferiority was therefore not demonstrated and the ESC considered that there were limitations with regards to the exchangeability of the trials.
- 6.16 The ESC noted that the proposed restriction allows for use of brexpiprazole in the acute and maintenance treatment settings. The submission did not provide any clinical evidence regarding the comparative efficacy or safety of brexpiprazole with aripiprazole in the maintenance setting.

**Indirect comparison: brexpiprazole versus lurasidone (acute setting)**

- 6.17 The submission claimed non-inferiority in terms of efficacy. The results of the indirect comparison between brexpiprazole and lurasidone in the acute setting in terms of the total PANSS score were not statistically significant (LOCF: 0.8 (-3.573, 5.173),  $p=0.720$ ) and (MMRM: 3.49 (-1.319, 8.299),  $p=0.155$ ). Although the mean difference in the outcomes did not reach the MCID, the upper limit of the 95% CI for the differences between the two treatment groups was above 7 points in the MMRM analysis, which indicates that a difference in favour of lurasidone cannot be excluded. The ESC considered that there were limitations with regards to the exchangeability of the trials.

**Indirect comparison: brexpiprazole versus lurasidone (maintenance setting)**

- 6.18 The indirect comparison of time to relapse/impending relapse was statistically in favour of brexpiprazole compared to lurasidone. The clinical significance of this finding was highly uncertain given the different definitions of the primary outcome between the two trials. The mean change in the PANSS total score was not statistically significant (-3.85 (-10.186, 2.486);  $p=0.234$ ; LOCF analysis). The PSCR states that while the definition of 'relapse' differed slightly across the trials, clinical expert opinion is that both definitions use validated rating scales for psychopathology and cover the same and appropriate domains (such as aggression and suicidality), and both included hospitalisations, and that these similarities indicate that the results will be comparable across the trials. The ESC considered that the claim of non-inferiority (efficacy) was uncertain given the different definitions of the primary outcome between the two trials.
- 6.19 In the pre-PBAC response, the sponsor again stated that four clinical experts were consulted and they indicated that although there were differences in the definition of relapse criteria, from a clinical perspective, they were sufficiently similar to enable a valid comparison between the two studies.

**Comparative harms**

- 6.20 The submission presented safety data based on the direct comparison of brexpiprazole to aripiprazole in the acute setting. The submission claimed brexpiprazole was non-inferior to aripiprazole in terms of safety based on the adverse events reported during the 331-07-203 trial and the 331-13-008 trial.
- 6.21 Table 5 summarises the incidence of adverse events, serious adverse events (SAEs) and adverse events leading to withdrawal. None of the reported differences were statistically significant, which may be due to the post-hoc nature of the comparison between brexpiprazole and aripiprazole, and the small sample size of the trials.

**Table 5: Summary of treatment emergent adverse events in the direct randomised trials**

Trial ID	Brexpiprazole n with event/N (%)	Aripiprazole n with event/N (%)	OR (95% CI)	RD (95% CI)	RR (95% CI)
<b>331-13-008</b>					
Any adverse event	37/64 (57.8%)	21/33 (63.6%)	0.78 [0.33, 1.86]; P=0.58	0.91 [0.65, 1.27]; P=0.57	-0.06 [-0.26, 0.15]; P=0.58
SAE	3/64 (4.7%)	1/33 (3.0%)	1.57 [0.16, 15.75]; P=0.70	1.55 [0.17, 14.30]; P=0.70	0.02 [-0.06, 0.09]; P=0.68
AEs leading to withdrawal	3/64 (4.7%)	1/33 (3.0%)	1.57 [0.16, 15.75]; P=0.70	1.55 [0.17, 14.30]; P=0.70	0.02 [-0.06, 0.09]; P=0.68
<b>331-07-203</b>					
Any adverse event	57/90 (63.3%)	35/50 (70.0%)	0.74 [0.35, 1.55]; P=0.43	0.90 [0.71, 1.15]; P=0.41	-0.07 [-0.23, 0.09]; P=0.42
SAE	5/90 (5.6%)	2/50 (4.0%)	1.41 [0.26, 7.56]; P=0.69	1.39 [0.28, 6.90]; P=0.69	0.02 [-0.06, 0.09]; P=0.67
AEs leading to withdrawal	5/90 (5.6%)	3/50 (6.0%)	0.92 [0.21, 4.03]; P=0.91	0.93 [0.23, 3.71]; P=0.91	0.00 [-0.09, 0.08]; P=0.91

Source: Table B.6.2, of the commentary. Abbreviations: SAE = serious adverse events; AE = adverse events; OR = odds ratio; RR = risk ratio; RD = risk difference

- 6.22 The frequency of treatment-emergent adverse events (TEAEs) reported in trial 331-13-008 with occurrence of  $\geq 5\%$  in the brexpiprazole arm were: weight gain (9.4%), akathisia (9.4%), dry mouth (7.8%), dyspepsia (7.8%), headache (7.8%), nausea (6.3%) and pain in extremity (6.3%). TEAEs reported in the aripiprazole arm were: akathisia (21.2%), headache (12.1%), constipation (9.1%), dyspepsia (9.1%), weight gain (9.1%), diarrhoea (6.1%), dry mouth (6.1%), toothache (6.1%), back pain (6.1%), muscle spasm (6.1%) and sedation (6.1%). In trial 331-07-203, the frequency of the TEAEs which occurred with an incidence of  $\geq 5\%$  in the brexpiprazole (2.5  $\pm$  0.5 mg) arm were: headache (14.4 %), weight gain (10%), nausea (7.8%) and akathisia (5.6%). In trial 331-07-203, TEAEs which occurred with an incidence of  $\geq 5\%$  in the aripiprazole arm were: weight increase (6%), headache (6%), restlessness (6%), diarrhoea (8%) and agitation (10%).
- 6.23 None of the results (for changes from baseline to endpoint) on extrapyramidal symptom, Barnes akathisia rating scale, abnormal involuntary movement scale and

body weight changes were statistically significantly different (between groups or from baseline).

- 6.24 Evaluation of the prolactin changes in patients favoured brexpiprazole and were statistically significant in both trials (331-07-203,  $p = 0.04$ ; and 331-13-008,  $p=0.005$ ). The submission stated that the differences were small and not clinically relevant. This is supported by the conclusions from the TGA Round 2 Clinical Evaluation Report that changes in prolactin from baseline to last visit across all treatment groups were small and none of the changes were considered to be clinically meaningful.
- 6.25 On the basis of the direct comparison, the frequency of adverse effects with brexpiprazole and aripiprazole appears to be similar, although this may be due to the small sample size of the trials and the post-hoc nature of the analysis.

### **Clinical claim**

6.26 Aripiprazole

The submission did not make any claim or provide any clinical evidence regarding the comparative efficacy or comparative safety of brexpiprazole compared to aripiprazole in the maintenance setting.

The submission described brexpiprazole as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over aripiprazole in the acute setting. The clinical claim is based on two direct comparisons and one indirect comparison.

Given the available data, the ESC considered claim may be reasonable with respect to comparative safety, but uncertain with respect to comparative effectiveness. The ESC noted the following issues:

#### Direct comparison

- In trial 331-07-203 there was no statistically significant difference in the mean change in PANSS total score; however, the upper bound of the 95% confidence interval exceeds the MCID of 7, previously accepted by the PBAC, and favours aripiprazole.
- In trial 331-13-008 the upper bound of the 95% confidence interval for the difference in the mean change in PANSS total score was less than 7, but this was an open-label study and as such potentially subject to bias.
- Comparisons of brexpiprazole with aripiprazole in both trials relied on small patient numbers and were post-hoc.
  - The ESC noted that the PBAC has consistently used 7 points as the MCID on the PANSS Scale in previous considerations of other medicines for schizophrenia (paliperidone PSD, November 2007, lurasidone PSD, March 2015).

#### Indirect comparison

- The results of the indirect comparison between brexpiprazole and aripiprazole in terms of the mean change in PANSS total score were statistically in favour of aripiprazole 4.31 (95%CI: 1.351; 7.269,  $p = 0.004$ ) (based on the LOCF analysis). Although the mean difference in the outcomes did not reach the MCID,

the upper limit of the 95% CI for the differences between the two treatment groups was above 7 points, which indicates that a clinically significant difference in favour of aripiprazole cannot be excluded.

- The results of the sensitivity analyses of the PANSS total score also showed two statistically significant outcomes favouring aripiprazole. First, by excluding two aripiprazole studies which enrolled patients with schizoaffective disorder (27.5% and 29.4% of patients respectively) the difference in PANSS total score was statistically significant, favouring aripiprazole. Second, a sensitivity analysis of the indirect comparison between brexpiprazole and aripiprazole, including data from only the brexpiprazole arm from the 331-07-203 trial, was statistically significant in favour of aripiprazole, PANSS total score (5.03 (95% CI: 1.952, 8.108),  $p = 0.001$ ).
- There are some limitations with the exchangeability due to differences in the baseline characteristics of participants, particularly differences in the proportion of male/female patients, the date of the trials and the duration of trials, with some trials having a six-week duration and some trials having a four week duration.
- There is evidence of a larger placebo response in brexpiprazole trials than in the aripiprazole which may indicate that the trials are not exchangeable.

6.27 The PBAC agreed with the ESC that the claim of non-inferior comparative effectiveness compared to aripiprazole was not adequately supported by the data.

6.28 The PBAC considered that the claim of non-inferior comparative safety compared to aripiprazole was reasonable.

6.29 Lurasidone

The submission describes brexpiprazole as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over lurasidone in the acute setting and maintenance setting. This claim is reasonable however the ESC noted the following issues:

Acute setting

- While the results of the indirect comparison between brexpiprazole and lurasidone in the acute setting in terms of the mean change in total PANSS score were not statistically significant, a clinically significant difference in favour of lurasidone cannot be excluded. Although the mean difference in the outcomes did not reach the MCID, the upper limit of the 95% CI for the differences between the two treatment groups was above 7 points in the MMRM analysis.
- There are some limitations with the exchangeability due to differences in the baseline characteristics of participants, particularly differences in the proportion of male/female patients, and differing eligibility criteria relating to the age of patients. The duration of treatment also varied across trials and four lurasidone trials did not report the mean duration of treatment.

Maintenance setting

- While the results of the indirect comparison of brexpiprazole and lurasidone in the maintenance setting in terms of the primary outcome (time to relapse/impending relapse) were statistically in favour of brexpiprazole compared to lurasidone the clinical significance of this finding is highly uncertain given the different definitions of the primary outcome between the two trials. The primary

outcome in Trial 331-10-232 was time to exacerbation of psychotic symptoms/impending relapse. The comparability of this outcome to the primary outcome in Tandon (2016) (time to relapse) is uncertain.

- The indirect comparison of the proportion of patients with impending relapse/relapse was also statistically in favour of brexpiprazole compared to lurasidone. As with the primary outcome, the clinical significance of this finding is highly uncertain given the different definitions of the outcome between the two trials.
- There are some limitations with the exchangeability due to differences in the baseline characteristics of participants, particularly difference in baseline severity of disease (as measured by the PANSS total score). In addition the lurasidone trials were older than the brexpiprazole trials. There is evidence of a larger placebo response in brexpiprazole trials than in the lurasidone which may indicate that the trials are not exchangeable.
- In the pre-PBAC response, the sponsor stated that the brexpiprazole trial (331-10-232) was terminated early on the basis of the positive results of the first of two pre-planned interim analyses. The lurasidone trial (Tandon 2016) similarly included two such pre-planned interim analyses after which the trial was to be terminated if efficacy was demonstrated. The lurasidone trial was not terminated early on that basis.
- In the pre-PBAC response the sponsor stated that baseline disease severity (at time of randomisation) were very similar across the trials with mean baseline PANSS total scores (SD) in 331-10-232 of 58.1 (8.1) for the placebo group and 56.5 (8.7) for the brexpiprazole group, compared with 54.4 across the lurasidone and placebo groups in Tandon 2016. The sponsor also argued that the dates of when the studies were conducted overlapped and that roughly the same proportion of patients in both the placebo arms experienced relapse.

6.30 The PBAC considered on balance that the claim of non-inferior comparative effectiveness compared to lurasidone was reasonable.

6.31 The PBAC considered that the claim of non-inferior comparative safety compared to lurasidone was reasonable.

### ***Economic analysis***

6.32 The submission presented a cost-minimisation analysis comparing brexpiprazole with lurasidone. The equi-effective doses were assumed to be 3.58 mg/day brexpiprazole and 80 mg/day lurasidone. This assumed dose relativity was not based on the clinical evidence comparing brexpiprazole and lurasidone. The dose of brexpiprazole (3.58 mg/day) was sourced from trial 331-13-008 while 80 mg/day of lurasidone was claimed to be a widely quoted dose. The dosage of lurasidone used in the lurasidone trials presented in the submission varied between 40 mg/day - 160 mg/day. The PSCR stated the dose for lurasidone was informed by the trial (Tandon et al 2016) used in the indirect comparison for the maintenance setting. The mean daily dose in this trial was 78.9 mg, although it only included patients who were successfully maintained on a dose of lurasidone of 40-80 mg daily. The PSCR further noted higher mean lurasidone doses in other trials noted in the lurasidone PSDs (125.5 mg in Trial 234; 86.3 mg in Study 231E).

- 6.33 In the pre-PBAC response the sponsor argued that if considered more appropriate, by the PBAC, the dose of brexpiprazole used in the long-term maintenance trial (331-10-232) may be used to inform the calculation of equi-effective doses. The mean modal daily dose of brexpiprazole would be 3.58 mg and the mean daily dose of lurasidone would be 78.9 mg of lurasidone (taken from Tandon 2016).
- 6.34 The PBAC considered that the equi-effective doses were brexpiprazole 3.58 mg/day and 78.9 mg/day for lurasidone.
- 6.35 In the pre-PBAC response the sponsor proposed a flat pricing structure. The cost-minimising price of brexpiprazole compared to lurasidone was calculated as DPMQ \$141.84. This is summarised in the table below.

**Table 6: Cost-minimising brexpiprazole versus lurasidone**

	Ex-man / tablet	PtP / tablet	Pack cost, ex-man	Pack cost, PtP	Pack cost, DPMQ
<b>Original submission: equi-effective doses Brexpiprazole 3.58 mg = Lurasidone 80 mg</b>					
Brexpiprazole 1 mg x 30	\$	\$	\$	\$	\$
Brexpiprazole 2 mg x 30	\$	\$	\$	\$	\$
Brexpiprazole 3 mg x 30	\$	\$	\$	\$	\$
Brexpiprazole 4 mg x 30	\$	\$	\$	\$	\$
<b>Pre-PBAC: equi-effective doses Brexpiprazole 3.567 = Lurasidone 78.9 mg</b>					
Brexpiprazole 1 mg x 30	\$	\$	\$	\$	\$
Brexpiprazole 2 mg x 30	\$	\$	\$	\$	\$
Brexpiprazole 3 mg x 30	\$	\$	\$	\$	\$
Brexpiprazole 4 mg x 30	\$	\$	\$	\$	\$

Source: compiled based on pre-PBAC response p3. Abbreviations: DPMQ, dispensed price for maximum quantity; PtP, price to pharmacist; Note: Dispensing fee = \$7.02

**Drug cost/patient/year**

- 6.36 In the pre-PBAC response the sponsor stated the revised drug cost per patient per year is \$ [REDACTED], calculated using the proposed DPMQ of \$ [REDACTED]. The PBAC noted that this calculation was verified by the Department, but produced a slightly different drug cost per patient per year of \$ [REDACTED], which was likely due to rounding.

**Estimated PBS usage & financial implications**

- 6.37 This submission was not considered by DUSC. The submission used a quasi-market share approach to estimate the net financial impact of including brexpiprazole on the PBS/RPBS. The number of prescriptions of brexpiprazole was estimated from the historical utilisation of paliperidone and ziprasidone in the first five years of their PBS listing. This method does not conform to the market-share approach suggested in the PBAC guidelines. The approach does not consider current market utilisation, or other therapies that are likely to be substituted in the market. The PSCR considers the employed approach was justified as the three most recently listed treatments with sufficient utilisation date, namely, ziprasidone, paliperidone and asenapine, all achieved similar levels of uptake in the first 4-5 years of listing.

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**Table 7: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Scripts of brexpiprazole					
Total scrips of substituted therapies					
Aripiprazole (50%)	5,374	11,065	13,996	15,097	17,793
Lurasidone (30%)	3,225	6,639	8,397	9,058	10,676
Asenapine (10%)	1,075	2,213	2,799	3,019	3,559
Olanzapine (10%) <sup>a</sup>	1,152	2,371	2,999	3,235	3,813
Total substituted therapies	10,825	22,288	28,191	30,410	35,840
<b>Estimated net cost to PBS/RPBS</b>					
Costs to PBS/RPBS, exclude co-payment, brexpiprazole	\$	\$	\$	\$	\$
Costs to PBS/RPBS, exclude co-payment, substituted therapies	-\$	-\$	-\$	-\$	-\$
Net cost to the PBS/RPBS with listing of brexpiprazole)	\$	\$	\$	\$	\$

Source: Table 142, p333; Table 143, p335; p144, p336 of the submission; Section E Brexpiprazole November 2016.xls<sup>a</sup> A relative pack size of 1.071 was considered in the calculation to account 30 days treatment

The redacted table shows that at year 5, the estimated number of brexpiprazole scripts was 10,000 – 50,000 and the net cost to the PBS/RPBS with listing of brexpiprazole was less than \$10 million per year.

- 6.38 The financial estimates are sensitive to the proposed list price of brexpiprazole and the assumed substitution rates. The majority of substitutions were assumed to be from relatively new agents, i.e. aripiprazole (50%) and lurasidone (30%), which was not fully supported by the analysis of PBS 10% data presented in the submission. Should more substitution occur from the lower price antipsychotic therapies, the net cost to the PBS/RPBS would increase.
- 6.39 The PSCR acknowledges that substitution with older-generation treatments such as olanzapine would increase the net PBS cost. A sensitivity analysis was presented in the PSCR with assumed substitution of 30% olanzapine (representing the older-generation treatments), 39% aripiprazole, 23% lurasidone and 8% asenapine, and the net PBS cost in year 5 increased to \$2.3 million. The ESC noted the 2016 Royal Australian and New Zealand College of Psychiatrists Guideline that suggests that brexpiprazole could substitute for a number of different antipsychotics.
- 6.40 In the pre-PBAC response the sponsor argued the use of the cost-minimising price versus lurasidone results in a negative cost to the PBS/RPBS and is therefore cost saving.

**Table 8: Sensitivity analysis for net PBS/RPBS cost for listing brexpiprazole on a cost-minimisation basis with lurasidone**

	Year 1	Year 2	Year 3	Year 4	Year 5
Base case	\$	\$	\$	\$	\$
Cost minimising price vs. lurasidone	-\$	-\$	-\$	-\$	-\$
Substitution rate <sup>1</sup>	\$	\$	\$	\$	\$

Source: compiled during evaluation, 1: Increased olanzapine (10%→20%) and paliperidone (0%→10%) substitutions and reduced aripiprazole (50%→30%) substitution

The redacted table shows that, at year %, the net PBS/RPBS save for listing brexpiprazole using the cost-minimising price versus lurasidone was less than \$10 million per year.

- 6.41 The PBAC noted the revised financial estimates and considered that any cost to the PBS/RPBS would only come from increased substitution of a drug with an inferior safety profile than brexpiprazole and was considered to be an acceptable outcome.
- 6.42 The submission did not consider the potential leakage into off-label use for the treatment of mania associated with bipolar-1 disorder. While this would be anticipated to increase the utilisation of brexpiprazole, the impact on the cost to the PBS is unclear because brexpiprazole may substitute for other treatments currently used for the treatment of bipolar-1 disorder.
- 6.43 In the pre-PBAC response the sponsor indicated there are no clinical trials of brexpiprazole for the treatment of bipolar-1 mania and that there are no plans to initiate such trials. The sponsor will therefore not be seeking TGA registration for this indication.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of brexpiprazole for the treatment of schizophrenia. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of brexpiprazole would be acceptable if it were cost-minimised against lurasidone. The PBAC accepted cost-minimisation on the basis of equi-effective doses of brexpiprazole 3.58 mg per day and lurasidone 78.9 mg per day.
- 7.2 The PBAC accepted lurasidone as the appropriate comparator.
- 7.3 The PBAC was satisfied that brexpiprazole is non-inferior in terms of efficacy and safety compared to lurasidone.
- 7.4 The PBAC noted that the requested PBS restriction is consistent with other PBS listed orally administered atypical antipsychotics.
- 7.5 The PBAC recommended that brexpiprazole should be treated as interchangeable on an individual patient basis with aripiprazole, lurasidone, paliperidone, and ziprasidone.
- 7.6 The PBAC advised that brexpiprazole is suitable for prescribing by nurse practitioners.
- 7.7 The PBAC recommended that the Early Supply Rule should apply.
- 7.8 The PBAC noted that this submission is not eligible for an Independent Review.

**Outcome:**  
Recommended

## 8 Recommended listing

### 8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
BREXPIRAZOLE Tablet 1 mg, 30	1	0		
BREXPIRAZOLE Tablet 2 mg, 30	1	5	Rexulti	Lundbeck Australia Pty Ltd
BREXPIRAZOLE Tablet 3 mg, 30	1	5		
BREXPIRAZOLE Tablet 4 mg, 30	1	5		

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Schizophrenia
<b>Restriction Level / Method:</b>	<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
<b>Administrative Advice</b>	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.

## 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.