

**5.20 VORTIOXETINE,  
tablets, 5 mg, 10 mg, 15 mg and 20 mg,  
Brintellix<sup>®</sup>, Lundbeck Australia Pty Ltd**

**1 Purpose of Application**

- 1.1 The major submission sought an Authority Required listing for the treatment of major depressive disorder in patients who have received and not responded to an initial antidepressant medication or patients who are intolerant of or who have contraindications to other initial antidepressant therapy.

**2 Requested listing**

- 2.1 The submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	No. of Rpts	Proprietary Name and Manufacturer	
VORTIOXETINE				
Vortioxetine 5 mg tablet, 28	1	5	Brintellix	LU
Vortioxetine 10 mg tablet, 28	1	5	Brintellix	LU
Vortioxetine 15 mg tablet, 28	1	5	Brintellix	LU
Vortioxetine 20 mg tablet, 28	1	5	Brintellix	LU

*\*Denotes published price. The submission sought a special pricing arrangement.*

<p><b>Authority required</b> Major depressive disorder</p> <p><b>Clinical criteria:</b> Patient must have received and not responded to an initial antidepressant medication OR Patient must be intolerant or contraindicated to other initial antidepressant therapy</p> <p><b>Population criteria:</b> Patient must be aged 18 years old or greater</p>
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*For more detail on PBAC's view, see section 7 "PBAC outcome"*

**3 Background**

- 3.1 Vortioxetine was TGA registered on 31 March 2014 for the treatment of major depressive disorder in adults including prevention of relapse.
- 3.2 Vortioxetine has not been considered by the PBAC previously.

**4 Clinical place for the proposed therapy**

- 4.1 The submission proposed that the intended use for vortioxetine is as an alternative drug treatment to be used after non-response to an initial therapy or lack of tolerability of an alternative therapy.

- 4.2 Several trials, presented in support of the proposed listing, did not exclude treatment-naïve patients. This suggests that vortioxetine may be prescribed as a first-line drug treatment.
- 4.3 The Pre-Sub-Committee Response (PSCR, pg.2) claimed that "...the treatment history recorded in the trials was in respect to the current major depressive episode (MDE). It is possible, even probable, that a considerable proportion of patients recorded as treatment naïve for their current episode were treatment experienced with respect to previous episodes". This did not clarify the issue of previous exposure to anti-depressants in the current episode.
- 4.4 The statement in the PSCR (pg.4) that "The submission proposes that vortioxetine belongs in the same place as agomelatine (not PBS funded), moclobemide and reboxetine" was not consistent with the use of desvenlafaxine as a comparator.

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

## **5 Comparator**

- 5.1 The submission nominated three comparators:
- Serotonin noradrenaline reuptake inhibitors (SNRI's) as the main comparator.
  - Selective serotonin reuptake inhibitors (SSRIs) as the secondary comparator.
  - Desvenlafaxine (an SNRI) as the comparator for the cost-minimisation analysis.
- 5.2 The ESC agreed with the evaluation that the use of SNRIs and SSRIs for the clinical comparison is appropriate but that the specific use desvenlafaxine to inform the economic comparison is not appropriate. The ESC considered that the comparator should be the therapy that prescribers would most replace with vortioxetine in practice. Therapeutic treatment guidelines and PBS claims data indicate there are a wide range of therapies that would be displaced in the treatment of MDD if vortioxetine was PBS listed. With the large number of currently PBS-listed selective serotonin reuptake inhibitors and other anti-depressant drugs (i.e. desvenlafaxine, venlafaxine, duloxetine, mirtazapine, reboxetine), the ESC considered that if a patient did not respond to one of these drugs initially, it would be likely that a patient would trial another drug within these groups of drugs. Given that vortioxetine's multimodal pharmacological activity appears to be predominantly related to serotonin (5-HT) regulation (see Product Information), the ESC considered that the comparator for the requested listing should be a weighted mean of SSRI use in MDD and 'Other antidepressants' (as listed in the PBS Schedule under 'Other antidepressants') use.

*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 No consumer comments were received for this item.

**Clinical trials**

- 6.3 The submission was based on four clinical comparisons:
- A direct comparison of vortioxetine and the SNRI therapies, conducted to provide evidence for the claim of non-inferiority compared to two SNRI therapies, venlafaxine and duloxetine.;
  - An indirect comparison of vortioxetine and the SNRI therapies, conducted to provide additional evidence in support of the claim of non-inferiority compared to the SNRI therapies;
  - An indirect comparison of vortioxetine and the SSRI therapies, conducted to provide evidence in support of the claim of non-inferiority compared to the SSRI therapies; and
  - An indirect comparison of vortioxetine and the SSRI therapies in the elderly, conducted to provide evidence of superiority compared to SSRI therapies in some patient populations.
- 6.4 The trials cited for the direct comparisons were the most relevant and are therefore listed below. The remaining trials used in the indirect comparisons are not listed due to the large number (see paragraphs 6.17-19).
- 6.5 Direct comparison: vortioxetine versus SNRI therapies (venlafaxine, duloxetine)  
 Details of the trials presented in the direct comparison of vortioxetine and the SNRI therapies are provided in the table below.

**Trials and associated reports presented in direct comparisons**

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Trials of vortioxetine and venlafaxine		
11492A	Double-blind, randomised, placebo-controlled study comparing the efficacy and safety of two fixed dosages of a novel antidepressant compound to that of placebo in patients with major depressive disorder.	2008
Alvarez E	A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder.	<i>Int J Neuropsychopharmacol</i> 2012, 15:589-600
Artigas F	A randomised, double-blind, placebo-controlled, active-referenced study of Lu AA21004 in patients with major depression.	<i>Eur Neuropsychopharmacol</i> 2009; 19:S426-7.
13926A	Randomised, double-blind, parallel-group, active-comparator (venlafaxine XR), fixed-dose study of Lu AA21004 in Major Depressive Disorder in Asian countries	2013

Trials of vortioxetine and duloxetine		
304	A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Active-Referenced, Fixed-Dose Study Comparing the Efficacy and Safety of 2 Doses of Lu AA21004 in Acute Treatment of Adults With Major Depressive Disorder	2010

Mahableshwarkar AR	A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder.	<i>Curr Med Res Opin</i> 2013; 29 (3):217-26.
315	A Phase 3, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Duloxetine-Referenced, Fixed-Dose Study Comparing the Efficacy and Safety of 2 Doses (15 and 20 mg) of Lu AA21004 in Acute Treatment of Adults With Major Depressive Disorder	2012
11984A	A randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study evaluating the efficacy and safety of three dosages of Lu AA21004, in acute treatment of Major Depressive Disorder	2010
Baldwin DS	A randomised, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD).	<i>Eur Neuropsychopharmacol</i> 2012; 22: 482-91.
Baldwin D	A randomised, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in MDD treatment.	<i>Eur Neuropsychopharmacol</i> 2011; 21: S390
12541A	Randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in acute treatment of Major Depressive Disorder in elderly patients	2011
Katona C	A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder.	<i>Int Clin Neuropsychopharmacol</i> 2012; 27(4): 215-23.
Katona C	A randomised, double-blind, placebo-controlled, active-referenced, study of the multimodal antidepressant of Lu AA21004 in treatment of elderly depressed patients..	<i>Eur Neuropsychopharmacol</i> 2012a; 22: S258-S259
13267A	A randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study evaluating the efficacy and safety of Lu AA21004 (15 and 20mg/day) in the acute treatment of adult patients with Major Depressive Disorder	2012
Boulenger JP	Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: A randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder.	<i>Int Clin Psychopharmacol</i> 2013.

6.6 All studies included in the direct comparison included patients who had not received any prior treatment for MDD.

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

### **Comparative effectiveness**

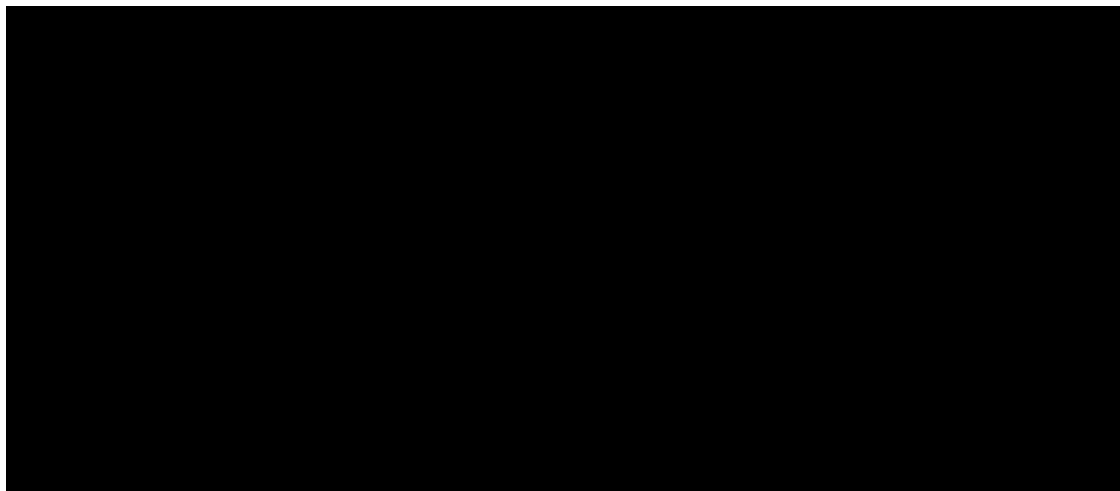
6.7 Results of the direct comparison of vortioxetine versus venlafaxine and duloxetine are shown in the table below:

**Results of mean baseline change in MADRS score (LOCF) across the direct randomised trials**

Trial	Vortioxetine mean change ± SD	Active comparator mean change ± SD	Mean difference (95% CI)
Trials of vortioxetine vs. venlafaxine			
11492A	-20.30 ± 10.45	-20.92 ± 10.48	0.62 (1.78,3.02)
13926A	-19.36 ± 10.12	-18.16 ± 9.97	-1.20 (-3.11,0.71)
Pooled result			-0.44 (-2.20,1.32)
Heterogeneity: Tau <sup>2</sup> = 0.43; Chi <sup>2</sup> = 1.35, df = 1 (P = 0.25); I <sup>2</sup> = 26%			
Test for overall effect: Z = 0.49 (P = 0.62)			
Trials of vortioxetine vs. duloxetine			
11984A			
12541A	-15.50 ± 9.34	-18.00 ± 9.25	2.50 [0.41, 4.59]
13267A			
304			
315			
Pooled result			
Heterogeneity: Tau <sup>2</sup> = 0.88; Chi <sup>2</sup> = 7.35, df = 4 (P = 0.12); I <sup>2</sup> = 46%			
Test for overall effect: Z = 3.72 (P = 0.0002)			

Abbreviations: SD = standard deviation, CI = confidence interval, df= degrees of freedom  
 Source: Table 28, p191 and Figure 9, p 193 of the submission

6.8 Results of the randomised trials comparing vortioxetine to venlafaxine and duloxetine are further summarised in the figure below:



Source: Figure 9, p 193 of the submission

- 6.9 In the comparison of vortioxetine versus venlafaxine there was no statistically significant difference between vortioxetine and venlafaxine. In the comparison with duloxetine, the pooled result was significantly in favour of duloxetine. The point estimate of the weighted mean difference (WMD) also exceeded the MCID (1.6 to 1.9) suggesting statistical and clinical significance of the outcome. The submission argued the clinical significance of the result was inconclusive as the 95%CI included the MCID (Treadwell et al 2012).
- 6.10 Baseline change using the HAM-D17 and HAM-D24 were consistent with the results using the MADRS.
- 6.11 Results using the HAM-D17 measure of effectiveness are shown in the table below:

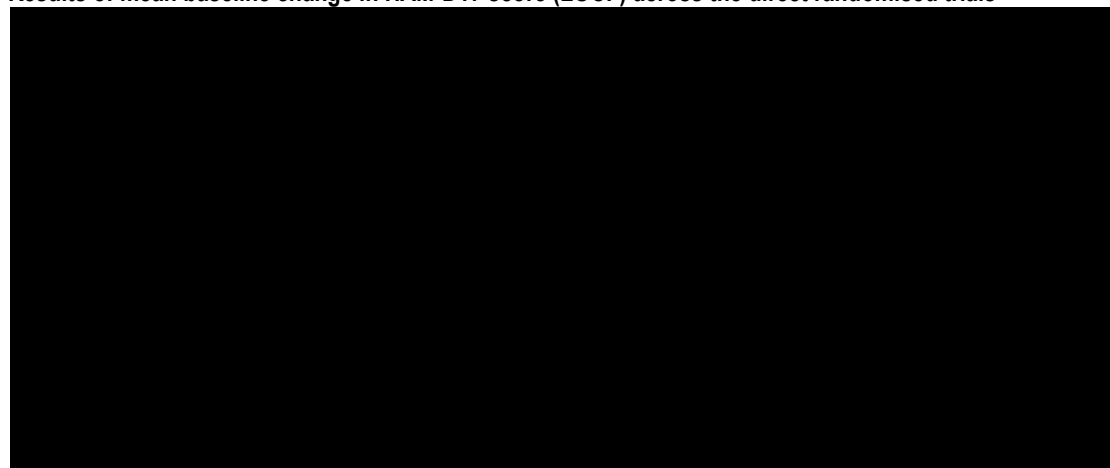
**Results of mean baseline change in HAM-D17 score (LOCF) across the direct randomised trials**

Trial	n	Vortioxetine mean change ± SD	Active comparator mean change ± SD	Mean difference (95% CI)
Trials of vortioxetine vs. venlafaxine				
11492A	319	-13.98 ± 7.44	-13.63 ± 7.48	-0.35 [-2.07, 1.37]
13926A		NR		
Pooled result				-0.35 [-2.07, 1.37]
Heterogeneity: NA Test for overall effect: Z = 0.40 (P = 0.69)				
Trials of vortioxetine vs. duloxetine				
11984A	455			
12541A	303			
13267A		NR		
304	302			
315		NR		
Pooled result				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.14, df = 2 (P = 0.57); I <sup>2</sup> = 0% Test for overall effect: Z = 2.66 (P = )				

Abbreviations: SD = standard deviation, CI = confidence interval, df= degrees of freedom  
Source: Table 30, p196 and Figure 11, p196 of the submission

- 6.12 Results using the HAM-D17 measure of effectiveness are further summarised in the figure below:

**Results of mean baseline change in HAM-D17 score (LOCF) across the direct randomised trials**



Source: Figure11, p 196 of the submission

- 6.13 Only one trial reported HAM-D17 scores when comparing vortioxetine to venlafaxine. The result was not statistically significant. In the comparison with duloxetine, the pooled result was significantly in favour of duloxetine. However, the point estimate of the WMD did not exceed the MCID of 1.5.
- 6.14 Results using the HAM-D24 measure of effectiveness are shown in the table below:

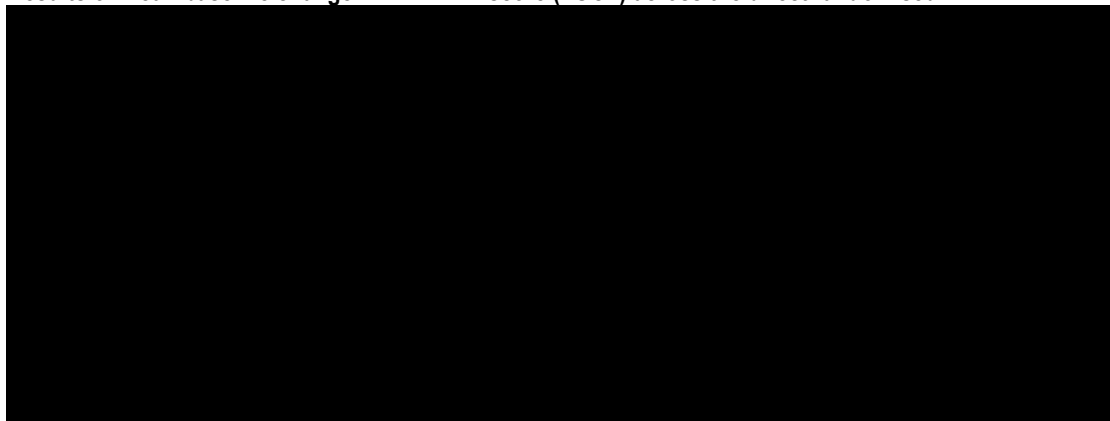
**Results of mean baseline change in HAM-D24 score (LOCF) across the direct randomised trials**

Trial	n	Vortioxetine mean change ± SD	Active comparator mean change ± SD	Mean difference (95% CI)
Trials of vortioxetine vs. venlafaxine				
11492A	319	-17.54 ± 9.23	-17.32 ± 9.27	-0.22 [-2.35, 1.91]
13926A	NR			
Pooled result				-0.22 [-2.35, 1.91]
Heterogeneity: NA Test for overall effect: Z = 0.20 (P = 0.84)				
Trials of vortioxetine vs. duloxetine				
11984A	455	██████████	██████████	██████████
12541A	303	-13.70 ± 9.21	-15.80 ± 9.12	2.10 [0.04, 4.16]
13267A	NR			
304	302	██████████	██████████	██████████
315	NR			
Pooled result				██████████
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.12, df = 2 (P = 0.57); I <sup>2</sup> = 0% Test for overall effect: Z = 2.69 (P = ██████████)				

Abbreviations: SD = standard deviation, CI = confidence interval, df= degrees of freedom  
Source: Table 32, p198 and Figure 13, p199 of the submission

- 6.15 Results using the HAM-D24 measure of effectiveness are further summarised in the figure below:

**Results of mean baseline change in HAM-D24 score (LOCF) across the direct randomised**



Source: Figure13, p199 of the submission

- 6.16 Only one trial reported HAM-D24 scores when comparing vortioxetine to venlafaxine. The result was not statistically significant. In the comparison with duloxetine, the pooled result was significantly in favour of duloxetine. The MCID for the HAM-D24 was unknown.
- 6.17 Indirect comparison: vortioxetine versus SNRI therapies  
The comparison was based on an indirect comparison of 53 randomised trials and 60 placebo comparisons comparing vortioxetine to SNRIs, with placebo as the common comparator. There were no statistically significant differences between vortioxetine and the SNRIs (combined) for any of the reported outcomes. There were no statistically significant differences between vortioxetine and the SNRIs (individually) for any of the reported outcomes, except for remission on the MADRS scale, which was statistically in favour of venlafaxine. There were significant limitations to the indirect comparison in terms of exchangeability of the trials, including differences in dates of recruitment, differing inclusion criteria, differing baseline characteristics of

the patient populations and differing definitions of outcomes (trial definition of response and remission varied across trials).

6.18 Indirect comparison: vortioxetine versus SSRI therapies

The comparison was based on an indirect comparison of 79 randomised trials and 85 placebo comparisons comparing vortioxetine to SSRIs, with placebo as the common comparator. The results showed no statistically significant differences between the SSRI therapies (both individually and combined) and vortioxetine. Superiority of vortioxetine in terms of comparative effectiveness over the SSRIs was not demonstrated.

6.19 Indirect comparison: vortioxetine versus SSRI therapies in the elderly

The comparison was based on an indirect comparison of eight randomised trials and nine placebo comparisons comparing vortioxetine to SSRIs in elderly patients (aged ≥60 years), with placebo as the common comparator. Superiority of vortioxetine compared to the SSRIs was only demonstrated in three of the nine reported outcomes. In the remaining six outcomes, there were no statistically significant differences between vortioxetine and the SSRIs.

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

**Comparative harms**

6.20 Based on the direct randomised trials, the incidence of serious adverse events was similar for vortioxetine and venlafaxine, and also for vortioxetine and duloxetine. Treatment withdrawals due to adverse events were significantly more common in the venlafaxine arm than the vortioxetine arms. Treatment withdrawals due to adverse events occurred more frequently in the duloxetine arm than in the 5 mg and 10 mg vortioxetine arms and less frequently in the duloxetine arm than in the 15 mg and 20 mg vortioxetine arms, although this difference was not statistically significant.

6.21 A summary of the comparative benefits and harms for vortioxetine versus SNRI therapies is presented in the following table.

**Summary of comparative benefits and harms for vortioxetine and active comparator**

Benefits							
Continuous Outcome I: change from baseline MADRS scale (LOCF)							
	Vortioxetine			Active comparator			Mean difference*: Vortioxetine vs. active comparator (95% CI)
	n	Mean Δ baseline MADRS	SD	n	Mean Δ baseline MADRS	SD	
Trials of vortioxetine vs. venlafaxine							
11492A	208	-20.30	10.45	112	-20.92	10.48	0.62 (1.78,3.02)
13926A	209	-19.36	10.12	215	-18.16	9.97	-1.20 (-3.11,0.71)
Pooled result							-0.44 (-2.20,1.32)
Heterogeneity: Tau <sup>2</sup> = 0.43; Chi <sup>2</sup> = 1.35, df = 1 (P = 0.25); I <sup>2</sup> = 26%							
Test for overall effect: Z = 0.49 (P = 0.62)							
Trials of vortioxetine vs. duloxetine							
11984A	306						
12541A	155	-15.50	9.34	148	-18.00	9.25	2.50 (0.41, 4.59)
13267A	243						
304	153						
315	292						
Pooled result							

Heterogeneity: Tau <sup>2</sup> = 0.88; Chi <sup>2</sup> = 7.35, df = 4 (P = 0.12); I <sup>2</sup> = 46%						
Test for overall effect: Z = 3.72 (P = [REDACTED])						
<b>Harms</b>						
	Vortioxetine (pooled dose)	Active comparator	RR (95% CI) <sup>^</sup>	Event rate/100 patients* <sup>^</sup>		RD (95% CI) <sup>^</sup>
				Vortioxetine	Active comparator	
<b>Trials of vortioxetine vs. venlafaxine</b>						
<b>Serious adverse events</b>						
11492A	2/208	1/113	1.09 (0.10,11.85)	0.96	0.88	0.00 (-0.01,0.01)
13926A	1/211	7/226	0.15 (0.02,1.23)	0.47	3.10	-0.03 (-0.06,0.01)
<b>Adverse events leading to withdrawal</b>						
11492A	10/208	16/113	0.34 (0.16, 0.72)	4.81	14.16	-0.14 (-0.39,0.11)
13926A	14/211	32/226	0.47 (0.26, 0.85)	6.64	14.16	-0.14 (-0.32,0.04)
<b>Trials of vortioxetine vs. duloxetine</b>						
<b>Serious adverse events</b>						
11984A	5/308	2/155	1.26 (0.25,6.41)	1.62	1.29	0.00 (-0.01,0.02)
12541A	1/156	1/151	0.97 (0.06, 15.34)	0.64	0.66	0.00 (-0.01,0.01)
13267A	1/302	3/147	0.16 (0.02, 1.55)	0.33	2.04	-0.02 (-0.04,0.01)
304	3/153	2/150	1.46 (0.25, 8.68)	1.96	1.33	0.01 (-0.02,0.03)
315	2/301	0/150	NA	0.66	0.00	0.01 (0.00,0.01)
<b>Adverse events leading to withdrawal</b>						
11984A	31/308	19/155	0.82 (0.48, 1.41)	10.06	12.26	-0.02 (-0.24,0.19)
12541A	10/156	15/151	0.65 (0.30, 1.39)	6.41	9.93	-0.04 (-0.21,0.14)
13267A	27/302	7/147	1.88 (0.84, 4.21)	8.94	4.76	0.04 (-0.08,0.16)
304	13/153	16/150	0.80 (0.40, 1.60)	8.50	10.67	-0.02 (-0.23, 0.18)
315	28/301	0/150	NA	9.30	0.00	0.09 (-0.01,0.19)

Abbreviations: SD = standard deviation, CI = confidence interval, df= degrees of freedom

<sup>^</sup>Calculated during the evaluation

\*Trial duration ranged from six to eight weeks. Source: Table 28, p191 and Figure 9, p 193 of the submission

6.22 On the basis of direct evidence presented by the submission, the comparison of vortioxetine and venlafaxine resulted in:

- No statistically significant difference in change on the MADRS scale over the trial period (six to eight weeks). It is considered that a reduction of 1.6 to 1.9 is clinically significant.

On the basis of direct evidence presented by the submission, the comparison of vortioxetine and duloxetine resulted in:

- A [REDACTED] increase (favouring duloxetine) in baseline change on the MADRS scale over the trial period (six to eight weeks). It is considered that a change of 1.6 to 1.9 is clinically significant.

- 6.23 Based on these trials and the most favourable results for vortioxetine, for every 100 patients treated with vortioxetine compared to venlafaxine:
- Up to 3 fewer patients would experience a serious adverse event (based on Trial 13926A)
  - Up to 9 fewer patients would experience an adverse event leading to withdrawal from treatment (based on Trial 11492A)
- 6.24 Based on these trials and the most favourable results for vortioxetine, for every 100 patients treated with vortioxetine compared to duloxetine:
- Up to 2 less patients would experience a serious adverse event (based on Trial 13267A)
  - Up to 4 less patients would experience an adverse event leading to withdrawal from treatment (based on Trial 12541A)
- 6.25 It was noted that the proposed price of vortioxetine was \$ [REDACTED] (for the highest strength, 20 mg) and the current price of the highest priced SNRI (desvenlafaxine 100 mg) is \$48.62. Therefore, vortioxetine was substantially more costly than alternative therapies. For vortioxetine to be PBS-listed at a substantially more costly price than an alternative therapy or alternative therapies, the PBAC noted that it needed to be satisfied that vortioxetine for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies under Section 101(3B) of the National Health Act 1953.

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

#### **Clinical claim**

- 6.26 The submission described vortioxetine as non-inferior in terms of comparative effectiveness and similar if not more favourable in terms of comparative safety over the SNRI therapies.
- 6.27 The submission also described vortioxetine as superior in terms of comparative effectiveness against the SSRI therapies in some patients (the elderly) and non-inferior if not more favourable than SSRI therapies in terms of comparative safety.

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

#### **Economic analysis**

- 6.28 The submission presented a cost-minimisation analysis comparing vortioxetine with desvenlafaxine. The cost minimisation analysis was based on [REDACTED] the [REDACTED] of 10 mg vortioxetine and 100 mg desvenlafaxine.
- 6.29 By cost-minimising vortioxetine to desvenlafaxine alone, the submission suggested that the price of vortioxetine could be made more commercially viable than a price based on a cost-minimisation listing against venlafaxine or duloxetine which the submission had noted to have been affected by statutory price reductions through generic competition. The ESC considered that this was not reasonable. The economic comparison should have reflected the current range of drugs likely to be displaced by vortioxetine.
- 6.30 The ESC advised that the submission should have used a weighted mean price of the drugs that would actually be displaced by vortioxetine. The ESC noted that the evaluation suggested that this could either be done using a weighted mean of SNRIs,

or a weighted mean of all alternative therapies (SSRIs, SNRIs, tricyclic anti-depressants and other anti-depressants). In the former case (i.e. using the SNRI class as the comparator) the submission estimated the weighted mean DPMQ of SNRIs (i.e. venlafaxine, desvenlafaxine and duloxetine) to be \$ [REDACTED], rather than the \$ [REDACTED] assumed in the submission. This represents a price reduction of [REDACTED]%. For all alternative therapies, the submission estimated the cost offset to be between [REDACTED]% of the cost of vortioxetine (with the small degree of variability driven by the changing share of the market for the different classes). These estimates suggested that, to achieve cost-equivalence relative to a weighted mean of all alternative therapies including second and subsequent line drugs, the proposed price of vortioxetine would have to fall by between [REDACTED] and [REDACTED]%. The ESC noted that a weighted mean of SSRIs and other anti-depressants (which would include the SNRIs but exclude tricyclics and monoamine oxidase A inhibitors) would likely equate to a price reduction for vortioxetine somewhere between the 2 estimates mentioned above (i.e. SNRIs or ‘all alternative therapies’) due to the low price of tricyclic anti-depressants.

- 6.31 The equi-effective doses were estimated as vortioxetine 10 mg daily and desvenlafaxine 100 mg daily.

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

**Drug cost/patient/year**

- 6.32 The drug cost per patient per year was \$ [REDACTED]. If the comparator is defined as all agents displaced, the cost/patient/year is between \$126.44 and \$130.39, with the variability caused by different market growth rates assumed for different classes of drugs.

**Estimated PBS usage & financial implications**

- 6.33 The submission was not considered by DUSC.
- 6.34 The likely number of prescriptions per year was estimated in the submission to be 1,138,981 in Year 5, at an estimated net cost per year to the PBS of \$ [REDACTED] in Year 5. The submission’s estimated PBS usage and financial implications are shown in the table below:

<b>Estimated use and financial implications</b>					
	<b>2014</b>	<b>2015</b>	<b>2016</b>	<b>2017</b>	<b>2018</b>
<b>Estimated extent of use</b>					
Total patient years (all anti-depressant classes)	800,608	838,182	873,067	904,444	932,351
Vortioxetine uptake	1.8%	4.9%	6.8%	8.4%	8.4%
Vortioxetine patient years	14,430	40,962	59,007	75,634	87,374
Prescriptions	188,108	533,968	769,202	985,940	1,138,981
<b>Estimated net cost to PBS/RPBS</b>					
Cost to PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<i>Offset costs from reduced use of other drugs</i>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Estimated total net cost</b>					
	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Tables 110 and 117 of the submission.

Figures in *italics* corrected during the evaluation to reflect current list prices for displaced agents

- 6.35 These figures were likely to under-estimate the actual financial implication of listing as the submission assumed no use in a treatment-naïve population, an unlikely assumption given the differing adverse event profile between vortioxetine and other agents.
- 6.36 The sponsor proposed a risk sharing agreement in the case that an ‘Authority Required’ listing was not considered appropriate. The sponsor proposed an aggregate spending cap to minimise the risk of leakage into those patients who are not intolerant or contraindicated to vortioxetine. The sponsor proposed to rebate the difference between the proposed price and the current generic weighted price of all the SNRI treatments for all spending on vortioxetine over this cap.

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

## **7 PBAC Outcome**

- 7.1 The PBAC rejected the submission on the basis that the clinical place of vortioxetine relative to SSRIs and SNRIs was unclear and that the claim of non-inferiority of vortioxetine compared to duloxetine was not adequately supported. Therefore, the cost-minimisation analysis against desvenlafaxine alone and the pre-PBAC response’s proposal to list vortioxetine on a cost-minimisation basis against a [REDACTED] SNRI class, were not accepted. In its consideration of the relevant comparator, the PBAC was of the view that there was insufficient reason to exclude SSRIs from an economic comparison which consequently did not support a cost-minimisation analysis of vortioxetine against a [REDACTED] SNRI class of drugs.
- 7.2 The PBAC noted the intent of the requested listing was to limit treatment to patients who had not responded to first line anti-depressant therapy but that interpreted literally, the requested listing would allow patients to receive vortioxetine after treatment with just one other anti-depressant therapy. The PBAC considered that first-line anti-depressant therapy could include SSRIs, SNRIs or anti-depressant therapies classed as ‘other’ in the PBS schedule and therefore the requested listing did not truly position vortioxetine as a second-line therapy.
- 7.3 The submission’s proposed the more restrictive ‘Authority required’ listing for patients who have failed other anti-depressant therapy in order to justify a higher listing price compared to existing SSRIs and SNRIs (including ‘other’ anti-depressant therapies such as duloxetine). The PBAC did not accept to use of an Authority required listing as a mechanism to justify a higher price relative to existing first-line anti-depressant therapies. The PBAC did not agree that such a listing would adequately limit treatment to a patient population in which vortioxetine would be most cost-effective. The PBAC considered that the requested listing should reflect vortioxetine’s clinical place in therapy.
- 7.4 The PBAC considered that the clinical place of vortioxetine in the treatment of depression was unclear for several reasons:
- Vortioxetine has only recently been TGA registered and therefore that there is limited clinical treatment experience with vortioxetine;
  - The pharmacology of vortioxetine was noted to be multimodal and appeared to be predominantly related to serotonin (5-HT) regulation, which suggested that it could be used in place of existing SSRIs;
  - In the trials presented in the submission, vortioxetine was not necessarily restricted to use in patients who had not responded to prior anti-depressant therapy; and

- Given the high number of existing PBS-listed SSRIs, SNRIs and other anti-depressants currently available on the PBS, vortioxetine may be substituted for SSRIs and not just recently listed therapies such as desvenlafaxine and duloxetine. This had implications for the choice of comparator in the economic comparison.
- 7.5 The submission's nominated comparator of SNRIs and SSRIs for the clinical comparison was considered appropriate, however the PBAC did not accept the use of the price of desvenlafaxine prior to the effects of statutory price reductions to derive a price for vortioxetine. The PBAC considered that the comparator, for both the clinical and economic comparison, should be the therapy most likely to be replaced in practice and that this may include SSRIs. The PBAC was of the view that there was insufficient reason to exclude SSRIs from an economic comparison and that unless further justification for excluding SSRIs from an economic comparison can be provided, any assessment of vortioxetine's cost-effectiveness would continue to have SSRIs as a relevant comparator for the economic comparison.
- 7.6 With respect to the clinical trials presented in the submission, the PBAC noted that the trial inclusion criteria for the direct comparison of vortioxetine to SNRI therapies did not necessarily limit vortioxetine treatment to patients who had not responded to prior anti-depressant therapy and therefore did not support the requested listing which attempted to position vortioxetine as second-line therapy. The PBAC further noted there were significant limitations to the indirect comparison of vortioxetine to SNRI therapies in terms of exchangeability of the trials, including differences in dates of recruitment, differing inclusion criteria, differing baseline characteristics of the patient populations and differing definitions of outcomes (trial definition of response and remission varied across trials).
- 7.7 The PBAC did not accept the submission's clinical claim of non-inferiority of vortioxetine to SNRI therapies. Based on the direct comparison of vortioxetine versus SNRI therapies, whilst there were no significant differences between vortioxetine and venlafaxine on any of the reported outcomes (changes in MADRS, HAM-D17, HAM-D24), non-inferiority of vortioxetine to duloxetine was not demonstrated. Meta-analyses comparing vortioxetine with duloxetine in terms of mean baseline change in MADRS, HAM-D17 and HAM-D24 scores favoured of duloxetine.
- 7.8 The submission's claim that vortioxetine is non-inferior compared to SNRIs in terms of safety was considered to be reasonable. The claim that vortioxetine may be more favourable than SNRIs in terms of safety was not clearly demonstrated when comparing higher doses (15 mg - 20 mg) of vortioxetine to SNRI therapies (at all doses) by the indirect comparison of total adverse events or withdrawals due to adverse events.
- 7.9 The submission's clinical claim that vortioxetine is superior in terms of comparative effectiveness against the SSRI therapies in some patients (elderly patients) and non-inferior if not more favourable than SSRI therapies in terms of comparative safety, was not accepted by the PBAC. The indirect comparison had significant limitations due to the lack of exchangeability of the trials. The indirect analysis conducted in a sub-group of elderly patients only demonstrated superiority of vortioxetine compared to the SSRIs in three of the nine reported outcomes. In the remaining six outcomes, there were no statistically significant differences between vortioxetine and the SSRIs.
- 7.10 Based on the trial evidence presented in the submission, the PBAC was not satisfied that vortioxetine provides a significant improvement in efficacy or reduction of toxicity

over venlafaxine, duloxetine, other SNRIs, other SSRIs and anti-depressants classified as 'other antidepressants' in the PBS schedule to warrant a price advantage.

- 7.11 The submission's cost-minimisation analysis of vortioxetine compared to desvenlafaxine and the pre-PBAC response's proposal to cost-minimise vortioxetine against the SNRI class of anti-depressants were not accepted. The PBAC was not satisfied that SSRIs could be excluded from the economic comparison, and considered that the non-inferiority of vortioxetine compared to the class of SNRIs had not been established, noting that trial results indicated that vortioxetine may be inferior to duloxetine.
- 7.12 The PBAC considered that the submission's estimated use of vortioxetine may have been underestimated since the clinical place of vortioxetine in the treatment of depression was unclear. The PBAC could not exclude the potential for vortioxetine to be prescribed in place of SSRIs as first-line therapy. The PBAC noted the reduced price offered in the pre-PBAC response and considered that the submission's estimated financial implications would be lower than originally estimated .
- 7.13 The PBAC considered that any resubmission should take the form of a major submission and provide further clarity on the expected clinical place of vortioxetine in the treatment of depression and a clinical need for vortioxetine therapy. Any resubmission should also provide further adequate justification for the chosen comparator, particularly for inclusion or exclusion of SSRIs from the economic comparison.
- 7.14 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

**8 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.

**9 Sponsor's Comment**

Lundbeck disagrees with the decision and believes there is a clear place for Brintellix in the clinical management of depression, especially where current treatments remain insufficient to improve depressed patients' quality of life. No new antidepressant has been listed on the PBS in more than five years, with six PBS submissions rejected in the last four years.

There is precedent in other therapeutic areas where therapies have been granted a second, third or later line PBS listing despite the supporting clinical evidence being from patient populations with treatment histories not necessarily consistent with such a listing. Lundbeck acknowledges that the proposed restricted listing to patients with insufficient response to initial antidepressant therapy is narrower than TGA-approved indication. Data supporting the efficacy of vortioxetine in the target population were presented in the submission.

Lundbeck would like to clarify that, in contrast to Section 6.18 above, the submission's clinical claim for vortioxetine was in fact one of non-inferior efficacy against the SSRI therapies, with superior efficacy in a subgroup of elderly patients.

Lundbeck would also like to clarify that although vortioxetine's pharmacology appears to be predominantly related to 5-HT regulation, the functional consequences on neurotransmission are significantly different from those observed with the SSRIs. Vortioxetine increases serotonergic, noradrenergic, dopaminergic, cholinergic and glutamatergic neurotransmission in brain structures associated with major depression, effects likely derived from its interaction with 5-HT-receptor-mediated negative feedback mechanisms controlling neuronal activity.

Regarding the direct clinical comparisons presented in the submission, Lundbeck refers to the European Medicine's Agency EPAR for vortioxetine (available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/human/002717/WC500159447.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002717/WC500159447.pdf)) which confirms that studies presented in the direct comparisons (with the exception of 13926A) were neither designed nor powered to show a treatment difference between vortioxetine and the active references venlafaxine and duloxetine. In each case, the active reference was included as internal control and the exclusion of non-responders and the inclusion of previous responders in the active reference arm could have introduced a bias in favour of the efficacy of the active reference, so differences in efficacy of vortioxetine versus the active reference cannot be inferred on the basis of these studies. These comparisons were provided to comply with PBAC guidelines; however, the data should be viewed in the context of its limited use to assess the relative effect of vortioxetine versus these comparators due to this bias. Indirect comparisons were presented to provide more information and represent the entire body of evidence for all medications. The indirect comparisons were completed in accordance with PBAC guidelines. Heterogeneity across trials is inherent in any meta-analysis and the evaluation has acknowledged that the approach taken by the submission to include all trials rather than split the trials was justified and reasonable.

Lundbeck regrets that beyond efficacy parameters, the PBAC evaluation of the clinical benefit does not reflect the improved safety and tolerability of Brintellix which are also key drivers of patient's quality of life and ultimately treatment compliance.

Given the significant burden depression continues to place on one in four Australians, access to innovative new treatment options is needed. Lundbeck will remain dedicated to demonstrating the value of Brintellix and will explore alternative options for bringing Brintellix to Australian patients.