NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Vortioxetine for treating major depressive disorder

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Company's decision problem

- The marketing authorisation for vortioxetine is for 'the treatment of major depressive episodes in adults'. The company made a case for the use of vortioxetine in a more narrow population (that is, people whose condition has not responded to initial treatment with a serotonin-specific reuptake inhibitors (SSRI) or serotonin–norepinephrine reuptake inhibitors (SNRI) and who wish to change antidepressant because of an inadequate response or intolerability to the initial treatment). The company refers to this population as the 'switch population'. The company considered that this reflects clinical practice of switching to an agent with a different mechanism of action. NICE's clinical guideline on Depression in adults (CG 90) states consider switching to:
    - initially a different SSRI or a better tolerated newer-generation antidepressant;

- subsequently an antidepressant of a different pharmacological class that may be less well tolerated, for example venlafaxine.

At what point in the treatment pathway is vortioxetine likely to be offered in England (for example, after first SSRI, after two or more SSRIs, after SSRIs as a pharmacological class have been exhausted etc.)?

- The company considered that based on NICE clinical guideline 90, its own market share data and clinical opinion, citalopram (SSRI), venlafaxine (SNRI), sertraline (SSRI), mirtazapine (non-SSRI/SNRI) and fluoxetine (SSRI) were the most relevant comparators. The company presented direct evidence for vortioxetine compared with agomelatine (non-SSRI/SNRI) and escitalopram (SSRI), and indirect evidence for vortioxetine compared with agomelatine, sertraline, venlafaxine, bupropion and citalopram. No comparisons were made by the company with duloxetine (SNRI; included in ERG's exploratory analyses), fluoxetine and mirtazapine. What are the most relevant comparisons?

Clinical effectiveness

- The ERG commented that the baseline severity of depression in the population enrolled into REVIVE was broadly representative of the 'switch population' in England but:
  - Most participants were white (99.8%) which is unlikely to reflect the 'switch population' in England;
  - 23% of all participants had received a SNRI as initial treatment which is not reflective of clinical practice in England, where their use first-line is negligible;
  - Most participants were recruited from an out-patient setting (97%);
  - The proportion of participants from the UK was small (≈7%).

  How generalisable are the results from the REVIVE trial to UK clinical practice?
- The company stated its indirect treatment comparison suggested vortioxetine is more efficacious and tolerable compared with other antidepressants in the proposed switch population. The company's indirect treatment comparison included 4 trials and 6 technologies, including vortioxetine (each arm of network was informed by 1 trial, see Figure 3). The trials included used different scales for measuring depressive symptoms and remission, and assessed outcomes at different time-points. The ERG stated that the heterogeneous nature of the data

meant that the company's indirect treatment comparison may not be reliable, and also the creation of a network relied upon the inclusion of Kasper et al. (2013) that may not have enrolled people only from the proposed 'switching' population.

  - Is the clinical evidence included in the company's indirect treatment comparison relevant for the company's proposed positioning of vortioxetine and its comparators (that is, after 1 SSRI therapy)?
  - How robust are the estimates of relative effectiveness obtained from the company's indirect treatment comparison?

- The ERG considered that there was substantial uncertainty associated with the company's indirect treatment comparison. The ERG identified 2 alternative data sources for estimating the relative effectiveness of vortioxetine with other antidepressants from the company's response to the ERG's and NICE's clarification request. These included meta-analyses of placebo-controlled trials with active reference arms in the non-switch population (that is, first-line population [Pae et al. 2014]) and an indirect treatment comparison in the non-switch population (Llorca et al. 2015). Of these sources, the ERG felt that Llorca may be the most reliable, although it had limitations because of the lack of direct comparison between active therapies.
  - Is evidence from the non-switching population relevant to inform relative effectiveness of vortioxetine compared with other antidepressants?
  - Is it plausible that the relative effectiveness of vortioxetine compared with (i) SSRIs, (ii) non-SSRIs, is similar between the non-switch and switch populations?
  - Which source, the company's indirect comparison, Pae or Lorca, is the most robust for estimating the effectiveness of vortioxetine compared with other antidepressants in people with major depressive disorder?
- The ERG concluded that based on the totality of evidence, vortioxetine is likely to be of similar efficacy as other antidepressants, but may be more efficacious than agomelatine but less efficacious than duloxetine for achieving remission.
  - What differences between rates of remission and depression severity scores (for example, MADRS) are considered clinically significant?

  - Is there sufficient evidence to robustly suggest a difference in effectiveness between vortioxetine and any of the comparators?

Cost effectiveness

- The company's model was a decision-tree that included a Markov component for subsequent switches to third and later treatment options. The ERG considered that the company's model structure was unnecessarily complicated and introduced inconsistencies between the timing of events in the decision tree and Markov component. Is the company's model structure appropriate?
- The company's model used remission data at 8-weeks from the trials to inform switching decisions at 4-weeks. The ERG noted that this not only excludes 4-weeks of treatment costs for non-remitters and overestimates the health benefits for remitters, but does not reflect how decisions are made in clinical practice because response is also a basis for treatment continuation.
  - Does the company's model adequately reflect clinical practice?
  - Was there evidence available for the company to model response?
- The company used the STAR*D trial, a prospective, sequentially randomized controlled trial of outpatients with nonpsychotic major depressive disorder comparing various switching or augmenting strategies, to inform rates of remission and relapse for subsequent switches after initial treatment in the model. The ERG stated that the population of STAR*D was not generalisable to the population of REVIVE and had lower rates of remission and higher rates of relapse than would be expected in clinical practice. The ERG stated that using STAR*D favoured the most effective initial switch treatment and potentially overestimated the length of a major depressive episode. Therefore, the ERG explored several scenarios around the remission and relapses rates for subsequent switches after initial treatment.
  - How long is an average major depression episode treated for?
  - What is the preferred approach for modelling remission and relapse of subsequent switches?
- The company used utility values from 2 different sources for the acute phase (REVIVE) and the maintenance phase (Sapin et al. 2004), see table 8. The ERG noted that the utility value from Sapin used by the company for non-remitters was

lower than utility value reported for non-remitters at 8-weeks in the REVIVE trial. Therefore, the ERG preferred to use utility values from REVIVE for both phases, see table 9. What is the most appropriate source for utility values?

- The company based doses in the acute and maintenance phases on the World Health Organisation Defined Daily Dose (for example, 10 mg daily for vortioxetine), and the mean dose reported at the end of trials included in its indirect treatment comparison, respectively. The ERG also explored a scenario in which the doses were the same for the acute and maintenance phases. Which dosing assumption is most appropriate?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of vortioxetine within its licensed indication for the treatment of major depressive disorder.

Table 1 Company's decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults with major depressive disorder	The company's decision problem addresses a **subset** of the population defined in the scope and marketing authorisation: "Adult patients with moderate-to-severe major depressive disorder who are experiencing an major depressive episode, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to an alternative antidepressant."	Selective serotonin reuptake inhibitors (SSRIs) are recommended as initial antidepressant therapy and all members of this class are now available as generics at low cost (less than £2 per month). Trials show vortioxetine to be suitable for depression that has failed initial SSRI or serotonin-noradrenaline reuptake inhibitor (SNRI) treatment. The company stated that these factors suggest vortioxetine is more likely to be cost-effective in switch use (that is, after initial treatment) rather than in initial use. The efficacy and tolerability profile of vortioxetine qualifies it as a "newer generation, better-tolerated antidepressant" particularly suitable for switch use as per NICE clinical guideline 90.	The ERG acknowledged the justification from the company. However, the ERG considered that this was an important limitation of the company's submission from a clinical and cost-effectiveness perspective (see 'comparators' section of table 1). The ERG was of the opinion that it would have been more appropriate for the company to include the full evidence base rather than restricting the decision problem to evidence in the switch population from the outset. Therefore, the ERG noted that uncertainty exists around the optimal position of vortioxetine in the treatment pathway.
Intervention	Vortioxetine		No comments	No comments.

Comparators	• selective serotonin reuptake inhibitors (for example citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) • tricyclic antidepressants (for example clomipramine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, and amitriptyline) • tricyclic-related antidepressants (for example mianserin and trazodone) • serotonin and noradrenaline reuptake inhibitors (for example venlafaxine, duloxetine and levomilnacipran) • other antidepressant drugs (for example agomelatine, mirtazapine, reboxetine and non-reversible mono-amine oxidase inhibitors [such as phenelzine]) • augmentation treatments (for example, with an antipsychotic such as quetiapine)	• agomelatine • citalopram • venlafaxine XL • sertraline • mirtazapine* • fluoxetine*	Based on its internal data, the company only included antidepressants with a UK second-line market share of 5% or more (source: Cegedim strategic data for the 12-month period April 2013-March 2014). Of these antidepressants, switch clinical data were available to support direct or indirect comparisons of efficacy and tolerability with agomelatine, citalopram, venlafaxine XL, sertraline. * No relevant data were identified by the company for mirtazapine or fluoxetine	Restricting the trial evidence to the switch population constrained the company's approaches to estimating the comparative efficacy. The restriction to consider only switch population evidence, and the small number of trials identified, meant that vortioxetine was compared directly only with agomelatine and escitalopram; and indirectly only with agomelatine, sertraline, venlafaxine (XR), bupropion and citalopram. No comparisons to duloxetine, fluoxetine or mirtazapine were made.

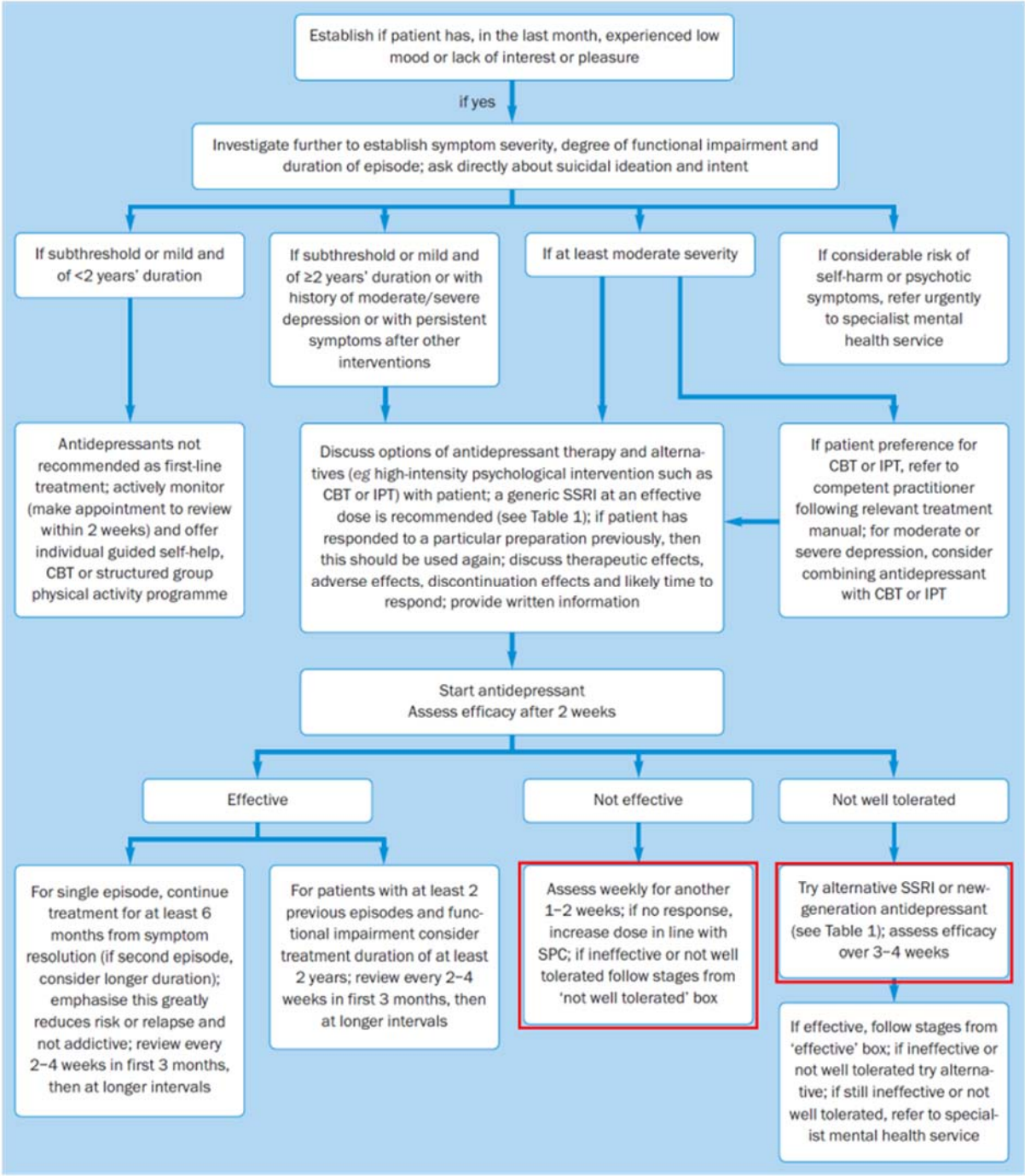
Outcomes	• response to treatment • relapse (including relapse rate and time from remission to relapse) • severity of depression • cognitive dysfunction • remission of symptoms • anxiety • sleep quality • hospitalisation • mortality • adverse effects of treatment • health-related quality of life.	The company stated it included all of these except mortality. In addition, the company stated it included outcomes of: • disability • family functioning • productivity (absenteeism and presenteeism).	Available clinical trial data are short-term (up to 1 year) and provide no direct evidence for longer-term course of major depressive disorder or differential mortality rates. The company considered that disability, family functioning, productivity are particularly relevant outcomes in major depressive disorder.	Outcomes measured in the short-term in trials. No data reported for relapse, cognitive dysfunction and sleep quality in REVIVE. No data on cognitive dysfunction, anxiety and sleep quality, or health-related quality of life outcomes (other than related to sexual dysfunction) reported in TAK318. Limited outcomes included in company's indirect treatment comparison (only 2: remission and withdrawal because of adverse reactions). In response to clarification, response and mean change from baseline were also presented by the company.
Other	If evidence allows, consider: • severity of depression (mild, moderate or severe) • clinical and cost effectiveness of vortioxetine in different positions in the treatment pathway.	Moderate-to-severe depression only. The cost-effectiveness analysis only considers the population indicated in the decision problem, that is, patients switching to switch antidepressant treatment.	The population for the decision problem is already limited by severity (moderate-to-severe) and by positioning (after inadequate response to an initial antidepressant). NICE CG90 step-care principle does not advocate use of antidepressants in mild depression (except persistent sub-threshold depression). No data are available for vortioxetine in mild depression.	The company's restriction to the switch population was potentially consistent with the "other considerations" section specified in the NICE scope.

2 The technology and the treatment pathway

2.1 Major depressive disorder is a broad and heterogeneous condition associated with a range of cognitive, behavioural, emotional, and physical symptoms. It is characterised by low mood and loss of pleasure in most activities. The severity of the disorder may vary from mild to severe depending on both the number of symptoms and the degree of functional impairment. In severe disease, psychotic symptoms may be present, and people may hallucinate or have delusions. Major depressive disorder often has a remitting and relapsing course, and symptoms may persist between episodes.

2.2 NICE guidance on Depression in adults (NICE clinical guideline 90; currently under review with expected date of publication May 2017) advocates a stepwise approach for managing major depressive disorder. NICE does not recommend routinely using antidepressants to treat mild major depressive disorder (hereafter called 'depression') except for people who have a past history of moderate or severe major depressive disorder or who have mild major depressive disorder that persists after other interventions. For people with moderate or severe depression, the guideline recommends combining an antidepressant medication and a high-intensity psychological intervention (cognitive behavioural therapy or interpersonal psychotherapy). NICE recommends that a clinician prescribes a generic selective serotonin reuptake inhibitor (SSRI) at first-line. Patients should be seen after 2 weeks of treatment and then every 2–4 weeks for the first 3 months. If the patient with depression develops side effects or his or her condition inadequately responds, NICE advocates switching to a different SSRI or a better tolerated newer-generation antidepressant may be considered (herein referred to as the "switch population"). If another treatment is subsequently needed, an antidepressant of a different pharmacological class may also be considered.

Figure 1 Interpretation of NICE CG90 recommended management & treatment pathway (Reid et al. 2014, Figure A5, page 36 of company's submission)



2.3 The company stated that based on the recommendations of NICE guidance on Depression in adults, clinical opinion and its UK market share data, the most commonly used treatments for the "switch population" (that is, after initial treatment) are: sertraline, mirtazapine, citalopram, fluoxetine and venlafaxine (see table 2).

Table 2 Overview of vortioxetine and its comparators for treating major depressive episodes

	Vortioxetine (Brintellix®)	Sertraline (Lustral®)	Mirtazapine (Zispin SolTab®)	Citalopram (Cipramil®)	Fluoxetine (Prozac®)	Venlafaxine (Efexor® XL)
(related) Marketing authorisation	• major depressive episodes in adults	• major depressive episodes • prevention of recurrence of major depressive episodes	• episodes of major depression	• major depressive episodes	• symptoms of depressive illness, with or without associated anxiety symptoms, especially where sedation is not required	• treatment of major depressive episodes • prevention of recurrence of major depressive episodes
Administration	All technologies are orally administered					
Posology	Initially 10 mg daily in adults less than 65 years of age. Adjustments are made based on response & tolerability.	Initially 50 mg daily, increased if necessary by increments of 50 mg at intervals of at least 1 week to max. 200 mg daily.	Initially 15–30 mg daily at bedtime increased within 2–4 weeks according to response; max. 45 mg daily.	Initially 20 mg once daily increased if necessary in steps of 20 mg daily at intervals of 3–4 weeks; max. 40 mg daily.	Initially 20 mg daily increased after 3–4 weeks if necessary, and at appropriate intervals thereafter; max. 60 mg daily.	Initially 75 mg daily in 2 divided doses increased if necessary at intervals of at least 2 weeks; max. 375 mg daily.
Cost	5 mg x 28: £27.72 10 mg x 28: £27.72 20 mg x 28: £27.72	50 mg x 28: £17.82 100 mg x 28: £29.16	15 mg x 30: £15.06 30 mg x 30: £15.06 45 mg x 30: £15.06	20 mg x 28: £8.95	20 mg x 30: £1.50	37.5 mg x 56: £2.32 75 mg x 56: £2.59 Modified release: 75 mg x 28: £22.08 150 mg x 28: £36.81

Source: Company's submission and British National Formulary (March 2015). XL, extended release.

See vortioxetine's summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 No statements from professional or patient groups were submitted to NICE.

4 Clinical-effectiveness evidence

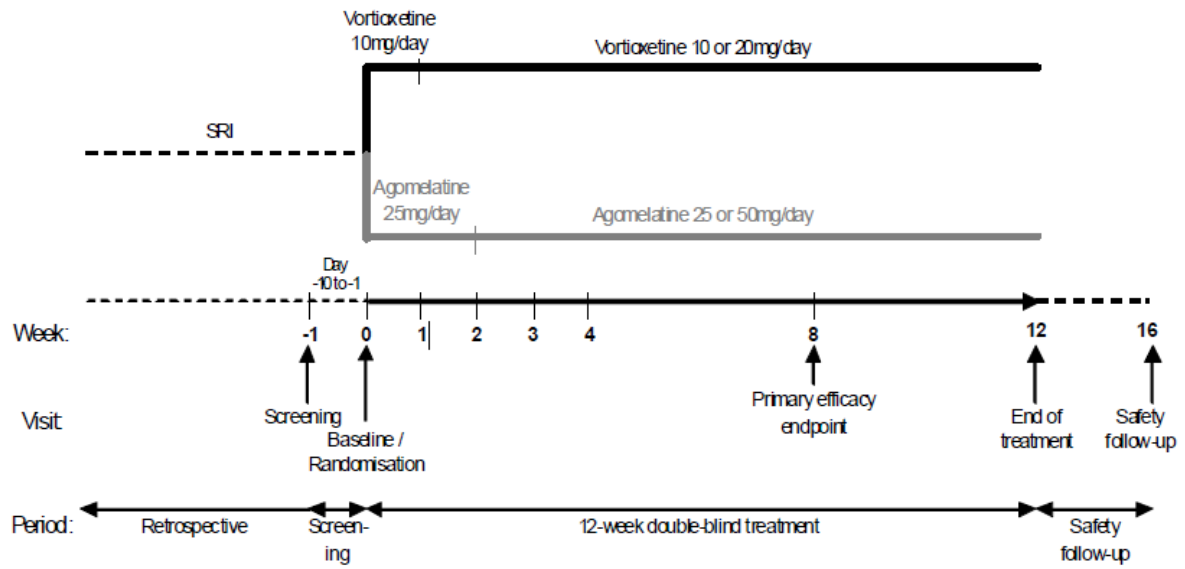
Overview of the clinical trials

4.1 The company conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of vortioxetine for treating adults experiencing a moderate-to-severe major depressive episode, whose condition has responded inadequately or has not tolerated the initial antidepressant treatment, and requires further antidepressant therapy (hereafter referred to as the 'switch population'). The company did not consider all adults with major depressive disorder as specified in NICE's final scope and vortioxetine's marketing authorisation. It identified 2 phase III randomised controlled trials, REVIVE and TAK318.

4.2 REVIVE was an international (14 European countries including those in the UK), double-blind, randomised active-control trial in 495 adults with moderate-to-severe major depressive disorder whose condition had inadequately responded to monotherapy with a serotonin reuptake inhibitor (SRI) [see Figure 2]. Patients were randomised 1:1 to flexible doses of vortioxetine (10–20 mg daily; starting dose 10 mg daily), or agomelatine (25–50 mg daily; starting dose 25 mg daily). Patients were assessed weekly during the first 4 weeks of treatment and then every 4 weeks until the end of the 12-week treatment period. A further safety assessment was scheduled 4 weeks after completion or withdrawal from the study. Most patients enrolled into REVIVE were women (74.7%) or white (99.8%), with a mean age of 46.3 years and a mean of 2.5 prior major depressive episodes. The company stated that both groups had comparable baseline Montgomery-Åsberg Depression Rating Scale (MADRS) scores and prior antidepressant use. Most patients received the

maximum dosage of vortioxetine (20 mg, 64.7%) and agomelatine (50 mg, 71.7%) from weeks 4–12.

Figure 2 Design of REVIVE (Figure B2, page 67 of the company's submission)



4.3 The primary outcome measure in REVIVE was change from baseline in MADRS score at week 8 (MADRS is a rating scale consisting of 10 items, each rated 0 [no symptom] to 6 [severe symptom] contributing to a total score from 0 to 60; the higher the score, the more severe the condition). A 'full analysis set' population (that is, people who were randomised into the study and had a baseline assessment and at least 1 post-baseline assessment) was used to analyse the efficacy outcomes. The company tested a hypothesis of non-inferiority using estimates from a mixed model for repeated measurements, which included treatment, week, and centre as fixed factors and the baseline MADRS score as a covariate. Non-inferiority was considered established if the upper bound of the two-sided 95% confidence interval of the difference between treatment groups in MADRS total score at week 8 did not exceed +2 MADRS units compared with agomelatine.

4.4 TAK318 was a multicentre (62 centres in USA and Canada), double-blind, randomised active-control trial in 447 adults with stable major depressive disorder experiencing treatment-emergent sexual dysfunction. Patients

were randomised 1:1 to flexible doses of vortioxetine (10–20 mg daily; starting dose 10 mg daily), or escitalopram (10–20 mg daily; starting dose 10 mg daily). Patients were assessed at the end of the 8-week treatment period and had an additional safety assessment 3 weeks after study completion. For further information about the participants and methods of TAK318, see pages 67–70 and 72–77 of the company's submission.

4.5 The primary outcome measure in TAK318 was change from baseline in the Changes in Sexual Functioning Questionnaire Short-Form 14 (CSFQ-14) total score after 8 weeks of treatment (total score ranges from 14 to 70; higher scores reflect higher sexual functioning). A 'full analysis set' population was used to analyse the efficacy outcomes based on a mixed model for repeated measurements of covariance (no formal hypothesis stated).

ERG comments

4.6 The ERG stated that the reporting of the company's searches were clear and appropriate. The ERG noted that the company presented no evidence to suggest the relative efficacy of non-selective SRIs may vary between initial and switch use. It concluded that it would be more appropriate to include the full evidence base for vortioxetine and its comparators, rather than restricting the evidence base from the outset to the switch population, and thereby excluding 22 of 24 completed studies of vortioxetine.

4.7 The ERG commented that REVIVE and TAK318 appeared well conducted but raised the following concerns:

- Both trials included comparators of limited relevance to clinical practice in England (for example, NICE has not issued any guidance for agomelatine; NICE technology appraisal 231 [terminated]).
- Both trials were short considering the duration of treatment recommended by NICE to achieve and consolidate remission, and so evidence of long-term efficacy was uncertain.

- Both trials evaluated the efficacy of vortioxetine 10-20 mg daily, so the efficacy of the licensed 5 mg daily regimen was uncertain.

4.8 The ERG commented that the population enrolled into REVIVE was broadly representative of the switch population in England. For example, baseline MADRS scores ranged from 22 to 43 points which is consistent with people experiencing moderate to severe major depressive disorder. However, the ERG noted that:

- Most participants were white (99.8%) which is unlikely to be reflective of the switch population in England.
- 23% of all participants had received a serotonin–norepinephrine reuptake inhibitor as initial treatment which is not reflective of clinical practice in England, where their use first-line is negligible.
- Most participants were recruited from an outpatient psychiatric setting (97.2%).
- The proportion of participants from the UK was small (approximately 7%).

4.9 The ERG noted that although the efficacy analyses in REVIVE and TAK318 used a modified intention-to-treat analysis (that is, full analysis set rather than inclusion of all randomised participants), the risk of bias was likely to be low because relatively few participants randomised were excluded.

Clinical trial results

REVIVE trial

4.10 The results of the primary outcome of REVIVE, the mean change from baseline in MADRS total score at week 8, were -16.5 and -14.4 points in the vortioxetine group and the agomelatine group respectively. This resulted in a mean difference of -2.16 points in favour of vortioxetine (95% confidence interval [CI] -3.51 to -0.81).

4.11 Pre-specified subgroup analyses of the primary outcome were carried out by the company for sex, age, baseline severity, baseline anxiety and class of prior antidepressant. The company stated that these analyses suggested vortioxetine improved MADRS score compared with agomelatine across all pre-specified subgroups. For further information, see pages 80, 92–3 of the company's submission.

4.12 The company stated that vortioxetine statistically significantly improved outcomes compared with agomelatine across the analyses of the secondary outcomes (see tables 3 and 4).

Table 3 Company's analysis of primary and secondary outcomes in REVIVE (Table B13, page 88 of company's submission; Table 12, ERG report)

Outcome	**Vortioxetine: difference compared with agomelatine**			
	Week 8		**Week 12**	
	MMRM	**LOCF, ANCOVA**	**MMRM**	**LOCF, ANCOVA**
Δ MADRS total score	-2.16*† (-3.51 to -0.81)	-3.1**	-2.03* (-3.45 to -0.60)	-3.5**
Δ HAM-A total score	-1.9**	-2.4**	-1.9**	-2.8**
Δ CGI-S score	-0.30* (-0.48 to -0.11)	-0.4**	-0.27* (-0.47 to -0.07)	-0.4**
Δ CGI-I score	-0.25* (-0.42 to -0.08)	-0.4**	-0.25* (-0.42 to -0.07)	-0.5**

Δ = mean change from baseline. † Primary efficacy analysis.
*p<0.01; **p<0.001 compared with agomelatine.
Vortioxetine: baseline n=252, week 8 n=220, week 12 n=200.
Agomelatine: baseline n=241, week 8 n=190, week 12 n=178.
ANCOVA, analysis of covariance; CGI-I, Clinical Global Impression - Improvement Scale; CGI-S, Clinical Global Impression - Severity Scale; HAM-A, Hamilton Anxiety Rating Scale; LOCF, last observation carried forward; MMRM, mixed model for repeated measures.

Table 4 Proportion of responders and remitters in REVIVE: FAS LOCF LREG (Table B14, page 89 of company's submission; Table 11, ERG report)

Outcome	Week 8				Adjusted OR (95% CI)	Week 12				Adjusted OR (95% CI)
	Vortioxetine		Agomelatine			Vortioxetine		Agomelatine		
	n	%	n	%		N	%	n	%	
Response										
MADRS	155	62%**	114	47%	1.81 (1.26 to 2.60)	176	70%**	135	56%	1.83 (1.26 to 2.65)
CGI-I	186	74%***	140	58%	2.03 (1.38 to 2.96)	187	74%*	154	64%	1.62 (1.10 to 2.39)
Remission										
MADRS	102	41%**	71	30%	1.72 (1.17 to 2.52)	139	55%***	95	39%	2.01 (1.39 to 2.90)
CGI-I	104	41%*	78	32%	1.55 (1.07 to 2.25)	140	56%**	106	44%	1.63 (1.14 to 2.33)

*p <0.05; **p <0.01; ***p <0.001 compared with agomelatine.
CGI-I, Clinical Global Impression - Improvement Scale; CI, confidence interval; FAS, full analysis set; LOCF, last observation carried forward; LREG, logistic regression; OR, odds ratio.

4.13 Health-related quality of life was measured at baseline and at weeks 4, 8 and 12 in the REVIVE trial using the EuroQol-5 dimensions survey (EQ-5D, see table 5). For the EQ-5D scores by status of remission, see pages 82–86 of the company's response to the clarification letter.

Table 5 EQ-5D summary scores and changes in EQ-5D score from baseline (Table B15 and Figure B9, page 91 of company's submission)

Assessment	Vortioxetine			Agomelatine			*p-value*
	n	Mean (SD)	Change from baseline*	N	Mean (SD)	Change from baseline*	
Baseline	252	0.53 (0.28)		241	0.55 (0.27)		
Week 4	241	0.70 (0.22)	0.16	233	0.64 (0.27)	0.08	<0.001
Week 8	220	0.76 (0.19)	0.20	189	0.73 (0.23)	0.16	0.03
Week 12	200	0.81 (0.21)	0.25	178	0.78 (0.22)	0.20	0.01

SD, standard deviation.
* Based on a mixed model for repeated measures analysis (see Figure B9 of company's submission).

TAK318 trial

4.14 Sexual functioning improved in both the vortioxetine and escitalopram groups, with a mean change from baseline in CSFQ-14 score at week 8 of +8.8 and +6.6 points respectively. This resulted in a mean difference of 2.2 points in favour of vortioxetine compared with escitalopram (p=0.013). For further results from the TAK318 study, see pages 96–99 of company's submission.

ERG comments

4.15 The ERG commented that the results from the company's analysis of the primary and secondary outcomes from REVIVE had relatively wide confidence intervals, and therefore the size of the difference in efficacy between vortioxetine and agomelatine was uncertain (see tables 3 and 4).

Indirect treatment comparison

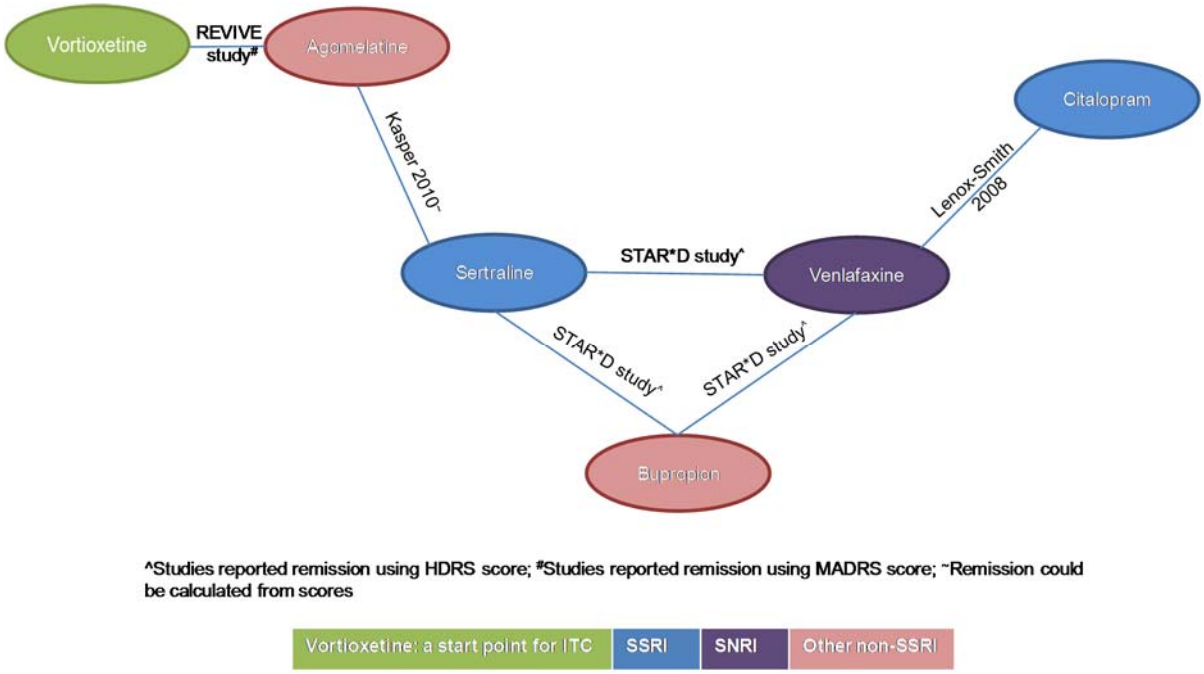
4.16 In the absence of head-to-head data comparing vortioxetine with comparators other than agomelatine in the switch population, the company conducted both a Bayesian indirect treatment comparison and a frequentist indirect treatment comparison using the Bucher method for 2 outcomes: rate of remission; and the proportion of people who stop treatment because of adverse reactions. The company systematically searched the literature and identified the REVIVE trial plus 3 additional multicentre blinded randomised controlled trials, which compared agomelatine with sertraline (Kasper et al. 2010), venlafaxine with citalopram (Lenox-Smith et al. 2008), and bupropion (which does not have a marketing authorisation in the UK for treating major depressive disorder) with sertraline and venlafaxine (STAR*D) [see Figure 3]. The company excluded:

- Rosso et al. 2012, which compared bupropion with duloxetine because it considered the method of randomisation (by day of the week) and blinding (single-blind) inadequate.

- 2 placebo-controlled trials, because the company's clinical advisers suggested that people who enroll in placebo-controlled trials may be different from those in active-controlled studies, but the company included these trials in a sensitivity analysis.

The company stated that its searches did not identify any evidence that allowed 2 other relevant comparators (fluoxetine or mirtazapine) to be included in the indirect treatment comparison.

Figure 3 Company's base-case network for the indirect treatment comparison (Figure B16, page 116 of the company's submission)



4.17 Kasper et al. (2013) was a post hoc analysis of the 'pre-treated' population from 2 trials of agomelatine in people with major depressive disorder. The number of patients enrolled in each of the 4 trials ranged from fewer than 100 (Kasper) to 789 (STAR*D). Mean age of patients was reported for 3 of the 4 trials and ranged from 41.8 (STAR*D) to 46.3 years (REVIVE). Baseline severity measured by HAM-D was between 21 (REVIVE) to >31 (Lenox-Smith et al. 2008) but the company considered that the differences between the trials would not have an impact on the treatment effect. In general, STAR*D enrolled a higher proportion of men

who were younger and whose depression was less severe than populations in the other trials. Outcomes were assessed at different time-points in the trials, from 6 weeks (Kasper) to 14 weeks (STAR*D). Each study measured depressive symptoms (and hence remission) using different scales: MADRS (REVIVE), HAM-D_{17} (Kasper, STAR*D) and HAM-D_{21} (Lenox-Smith) but the company stated that each trial used clinically accepted cut-off rates for remission which are generalisable regardless of the scale used.

4.18 The company stated the results of its indirect treatment comparison suggested vortioxetine works better and is better tolerated than the comparators. The results of the company's indirect treatment comparison are presented in tables 6 and 7. The company stated that it did not assess heterogeneity because of the small number of studies included in the network.

Table 6 Summary of the results of the company's frequentist indirect treatment comparison (Table 17, page 63 of the ERG report)

Treatment	Remission rate			People stopping treatment because of adverse reactions (withdrawal)		
	Rate (%)	Risk difference vs vortioxetine (%)	95% CI	Rate (%)	Risk difference vs vortioxetine (%)	95% CI
Vortioxetine	40.5	–	–	5.9	–	–
Agomelatine	29.5	-11	-19.4 to -2.6	9.5	3.6	-1.1 to 8.3
Sertraline	26.1	-14.4	-29.9 to 1.1	18.0	12.1	3.1 to 21.1
Venlafaxine	33.3	-7.2	-24.3 to 9.9	18.2	12.3	0.8 to 23.8
Bupropion	29.8	-10.7	-27.8 to 6.4	24.2	18.3	6.4 to 30.1
Citalopram	23.7	-16.8	-41.1 to 7.5	18.0	12.1	-0.3 to 24.5
CI, confidence intervals.						

Table 7 Summary of the results of the company's Bayesian indirect treatment comparison (Table 18, page 63 of the ERG report)

Treatment	Remission rate			People stopping treatment because of adverse reactions (withdrawal)		
	Rate (%)	Odds ratio vs vortioxetine (%)	95% CrI	Rate (%)	Odds ratio vs vortioxetine (%)	95% CrI
Vortioxetine	40.5	–	–	5.9	–	–
Agomelatine	29.5	1.63	1.12 to 2.37	9.5	0.60	0.30 to 1.17
Sertraline	25.9	1.95	0.89 to 4.24	29.5	0.15	0.03 to 0.62
Venlafaxine	35.1	1.26	0.51 to 3.07	29.5	0.15	0.03 to 0.65
Bupropion	30.7	1.54	0.62 to 3.77	38.5	0.10	0.02 to 0.46
Citalopram	25.6	1.98	0.59 to 6.60	29.5	0.15	0.02 to 0.86
CrI, credible intervals.						

ERG comments

4.19 The ERG agreed with the company's assessment of bias for Rosso et al. (2012), so considered it was reasonable to exclude it, but noted it was the only trial that compared vortioxetine with duloxetine. The ERG stated that it was questionable whether Kasper et al. (2013) was suitable for inclusion in the indirect treatment comparison because it was unclear whether the population consisted entirely of patients who were switching treatments, or whether it also included those who had been treated for a previous depressive episode.

4.20 The ERG stated that it had significant concerns over the validity of the company's indirect treatment comparison because of the differences in the baseline patient characteristics and severity of depression of the populations across the 4 trials. It also stated that time of outcome assessment between trials (varying from 6 to 14 weeks) may also affect the results because rates of remission and withdrawal are likely to be time-dependent. The ERG concluded that the heterogeneous nature of data included in the network means that the results may not be reliable.

4.21 The ERG highlighted that there was little evidence of a statistically significant improvement in the efficacy for vortioxetine compared with the comparators, given that the results from the company's indirect treatment comparison had wide confidence intervals. It stated that the findings in

each specific trial drove the results of the company's indirect treatment comparison because of the sparse evidence network (that is, each arm of the network was informed by 1 trial). The ERG noted that basing results on risk differences was potentially inappropriate, because they may be sensitive to the heterogeneity across trials (see table 6), but acknowledged the company's results based on odds ratios were largely consistent (see table 7). The ERG also commented that the results from the company's sensitivity analysis including the 2 placebo-controlled trials were broadly similar to those that excluded them.

4.22 Because the ERG considered that there was no evidence to suggest the relative efficacy of non-selective SRIs varies between initial and switch use (see section 4.6), it sought from the company further evidence in a population at first-line treatment (that is, the 'non-switch population') during the clarification stage.

- The ERG re-analysed data from a published meta-analysis of placebo-controlled trials with active reference treatment arms (Pae et al. 2014). Pae compared vortioxetine with agomelatine (1 trial), duloxetine (5 trials) and venlafaxine (1 trial). The ERG noted that both the European Medicines Agency and the company have criticised the use of trials including active references because they are not true randomised comparisons given patients known to be non-responsive to the reference treatment are excluded, possibly biasing results in favour of the active reference. The ERG accepted the potential for such bias, but did not consider it substantial enough to exclude these trials. The ERG stated Pae found no evidence of any difference in efficacy between vortioxetine and venlafaxine, and that vortioxetine was worse thanduloxetine in terms of reducing depression scores, or achieving response and remission.
- Llorca et al. (2015) published an indirect treatment comparison that found no evidence of any difference in efficacy between vortioxetine and its comparators. Llorca identified placebo controlled trials of the following drugs: vortioxetine, agomelatine, desvenlafaxine, duloxetine,

escitalopram, sertraline, venlafaxine, vilazodone. The ERG commented that there was evidence to suggest fewer people stop vortioxetine because of adverse reactions than other treatments, including sertraline and venlafaxine. The ERG considered that Llorca may represent the most reliable evidence for comparing vortioxetine with other treatments.

For further information around the additional analyses in non-switch populations, see pages 23–60 of the company's response to the clarification letter and pages 72–78 of the ERG report.

4.23 The ERG concluded that based on the totality of evidence, vortioxetine is likely to be of similar efficacy as other antidepressants, but may be superior to agomelatine and inferior to duloxetine.

Adverse effects

4.24 The company presented short-term safety data from REVIVE. Approximately half of the patients in each treatment group had 1 or more treatment-emergent adverse reaction over the 12-week treatment period. Adverse reactions with an incidence of 5% or more for vortioxetine or agomelatine, respectively, were: nausea (16.2% and 9.1%), headache (10.3% and 13.2%), dizziness (7.1% and 11.6%) and somnolence (4.0% and 7.9%). Fewer patients in the vortioxetine group (1.2%) compared with the agomelatine group (1.7%) experienced serious adverse reactions. Fewer patients stopped treatment because of adverse reactions in the vortioxetine group (5.9%) than in the agomelatine group (9.5%).

4.25 The company also presented safety data from 5 open-label long-term extension studies including a total of 2587 patients, of which 54% were exposed to vortioxetine for 52 weeks or more. The overall incidence of treatment emergent adverse reactions was 74.6%, and was higher in the 15-20 mg dose group (78.9%) compared with the 2.5-10 mg group (71.2%).

4.26 For further adverse reaction data, see pages 93–5, 99 and 128–134 of the company's submission.

ERG comments

4.27 The ERG agreed that vortioxetine appears generally safe and tolerable in people with major depressive disorder. The ERG stated that although the incidence of adverse reactions was high in people taking vortioxetine, most were mild to moderate in nature, and there was no conclusive evidence that these were dose-dependent.

4.28 The ERG also concluded that vortioxetine may have a better overall safety profile than other antidepressants, but sparse comparative data for adverse reactions prevented the ERG making a firm conclusion.

5 Cost-effectiveness evidence

Model structure

5.1 The company did not identify any published studies of the cost effectiveness of vortioxetine for treating the 'switch population'. It submitted a decision tree model with a Markov component to include subsequent treatment switches to third and later lines (see Figures 4 and 5), and assumed a patient can be offered 1 of 5 treatments: vortioxetine, agomelatine, citalopram, sertraline and venlafaxine. The company conducted the economic analysis from an NHS and personal social services perspective and chose a time horizon of 12 months so did not discount costs and health effects. A half-cycle correction was applied to the health effects in the Markov part of the model (cycle length 2 months).

Figure 4 Company's decision-tree model (Figure B21, page 144 of the company's submission)

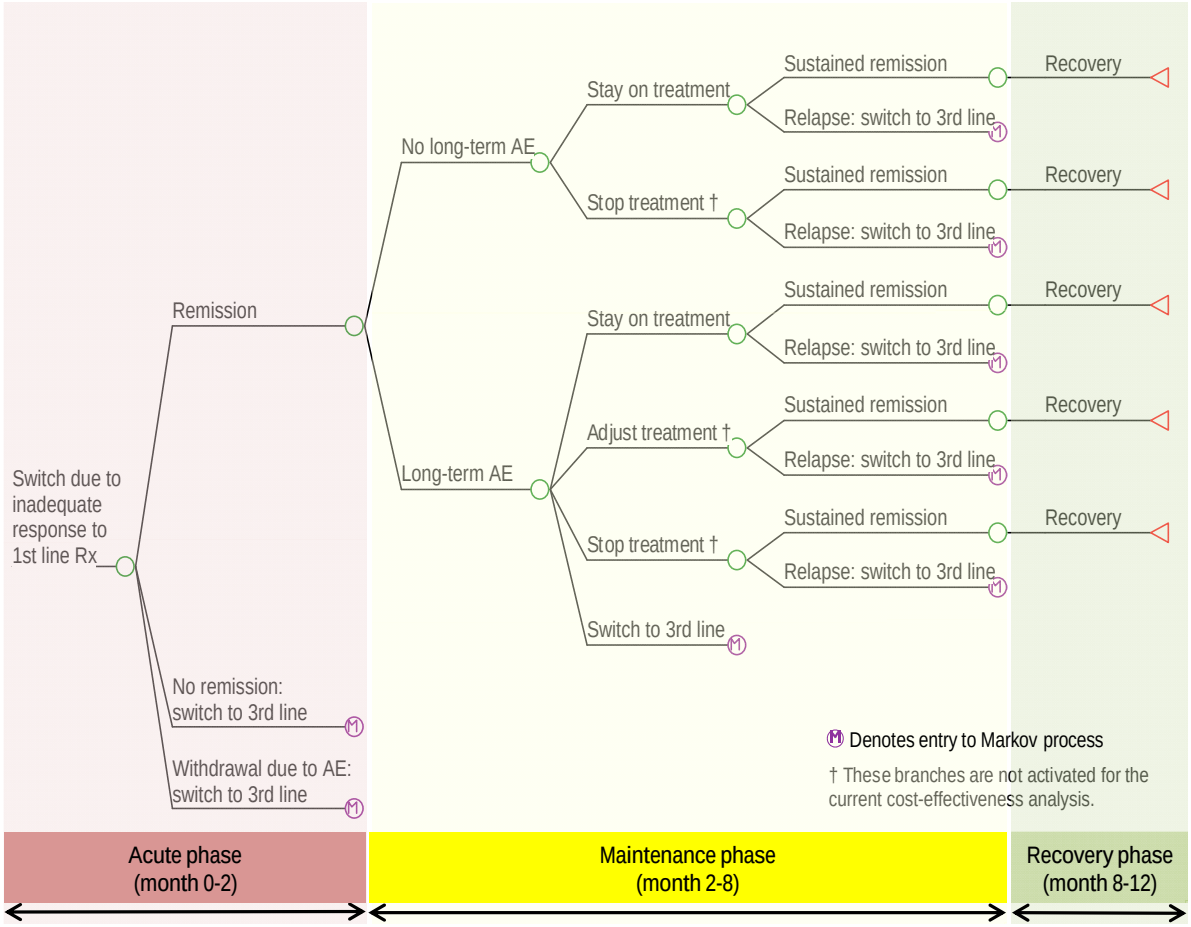
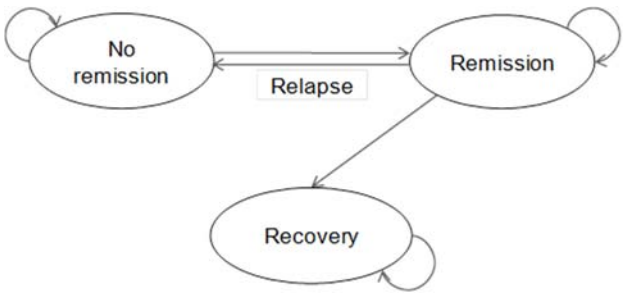


Figure 5 Markov component of company's economic model (Figure B22, page 145 of the company's submission)



5.2 The company stated its economic model represented a single major depressive episode. Hypothetical patients entered the model with major depressive disorder that had not responded to initial therapy. The decision tree included:

- an acute phase of treatment of 8 weeks (months 0–2)
- a maintenance phase of 6 months (months 2–8) and
- a recovery phase of 4 months duration (months 8–12).

The time patients spent in the decision tree varied and depended on whether treatment was successful in each phase. If treatment succeeded in all 3 phases, with remission achieved and sustained to recovery, a hypothetical patient spent the entire 12 months in the decision tree model. The company's economic model also included events in which treatment was not successful (lack of response or because of adverse reactions). These events led to a further switch, that is, to third-line treatment. Patients who did not complete the acute or maintenance phase left the decision tree model and entered the Markov component. In a given cycle of the Markov component, patients could either achieve remission or not. The company assumed that patients remained on treatment for 6 months after they achieved remission in the acute phase unless they experienced a long-term side-effect (insomnia, sexual dysfunction or weight gain).

ERG comments

5.3 The ERG stated that the company developed an unnecessarily complicated model structure. It was unclear why the company chose to:

- use different modelling approaches in the maintenance and recovery periods, rather than an initial decision tree for the acute phase and then a separate Markov component for all people in the subsequent 10 month period.
- assume in the maintenance phase different time-points for relapse (after 3 months) and stopping treatment because of adverse reactions (after 1 month) which favours those treatments with higher acquisition costs. The ERG noted that this introduced inconsistency between the timing of relapse for people within the decision tree and Markov components.

5.4 The ERG commented that basing the decision to switch treatments solely on remission data at 8-weeks was an important limitation. It stated that the company's model therefore excluded people whose condition responded to treatment, but who had not achieved full remission, and that in clinical practice, clinicians use response in deciding whether to continue treatments. The ERG commented that the company also used the 8-week remission data to inform switching decisions at 4-weeks in the model. The ERG explained that this ignores the costs of additional treatment for people whose disease responders (non-remitters) and may overestimate health benefits for people whose disease remits because it assigned a utility value based on improved health improvements demonstrated over 8 weeks rather than 4 weeks. The ERG concluded that the company's base case may underestimate vortioxetine's costs and overestimate vortioxetine's benefits.

5.5 The ERG noted the company's assumed that:

- Because in the recovery period, a person is not at risk of relapse or recurrence, this introduces a potential bias in favour of the most effective initial treatment. The ERG agreed that the risk of relapse may be different in later phases than in earlier phases of the condition, but that assuming no relapse seemed overly optimistic.
- patients remain on treatment for 6 months after remission in the maintenance phase was reasonable and consistent with Depression in adults, but was aware that NICE recommends 2 years of continued treatment in people considered high risk of relapse.

The ERG acknowledged that the company explored both of these assumptions in the company's response to clarification by varying the time-horizon of the model from 8 months [no recovery period] up to 2 years [treatment and monitoring costs continued in the recovery period]. The ERG concluded that although the company's base case analysis was robust to these scenarios, the ICER for vortioxetine compared with the next most cost-effective treatment was higher than in the company's base

case analysis, suggesting that including these assumptions potentially favoured vortioxetine. For further details of these scenario analyses, see pages 120–122 of the ERG report.

5.6 The ERG stated the company should have used a half-cycle correction for both costs and utility values, rather than for utility values only, since different health states are associated with different costs for consultation or hospitalisation.

5.7 The ERG highlighted that using a 12-month time horizon was reasonable for the 'average' patient because an untreated episode of major depressive order is estimated to last between 5 to 6 months (World Health Organisation 2008). However, the ERG noted that some people may be treated for longer than 12 months and therefore 12 months may not be sufficient to capture all of the relevant costs and consequences.

Model details

5.8 The company took data on the probability of remission after 8 weeks of treatment (acute phase) from its indirect treatment comparison (see table 6). The company assumed that an individual's probability of relapse during the 6 months of treatment after remission depended on the line of therapy rather than specific drug: initial switch treatment (14.2%, from Limosin et al. 2004), third-line (25.0%, from STAR*D[1]), fourth- and fifth-line (42.6%, from STAR*D). Patients who relapsed during the maintenance phase (which the company assumed occurred halfway

[1] STAR*D was a prospective, sequentially randomized controlled trial of outpatients with nonpsychotic major depressive disorder who received 1 (n=3671) to 4 (n=123) successive acute treatment steps. In level 1, participants received citalopram as their first treatment step. Level 2 and 3 treatments were randomly assigned. Level 2 provided 7 possible treatments involving 4 switch treatments (citalopram was stopped and new treatment initiated with sustained-release bupropion, cognitive therapy, sertraline or extended-release venlafaxine) and 3 augmentation options (citalopram plus bupropion, buspirone, or cognitive therapy). Level 3 included 2 medication switch strategies (mirtazapine or nortriptyline) or 2 medication augmentation strategies (lithium or T3 [25 mg]). Level 4 entailed only a single randomisation to either tranylcypromine or extended-release venlafaxine plus mirtazapine.

through the maintenance phase) could switch to third-line treatment. The company assumed that clinicians then assessed these patients for remission 2 months after starting third-line treatment, and took the data reflecting the proportion of patients in remission after each line of treatment from STAR*D: third- (13.7%), fourth- (13.0%) and fifth-line (13.0%). The company considered that patients who did not relapse after 6 months of maintenance treatment to have recovered. These patients stopped treatment and the company assumed that they could not experience recurrent depression.

5.9 Resource use and costs in the company's economic model included those for treatment (drug), adverse reactions and for each health state (that is, monitoring, inpatient and outpatient admissions). The company based drug costs on the list prices from the 'Monthly Index of Medical Specialities', and dosages in the acute on the World Health Organisation Defined Daily Dose (for example, 10 mg daily for vortioxetine), and dosages in the maintenance phase based on the mean dose reported at the end of trials included in the company's indirect treatment comparison. The company took data for health state resource use for the acute phases from an unpublished interim analysis of the PERFORM study (n=226, which included people on first-line treatment), and for the maintenance phase from Byford et al. (2011) General Practice Research Database 2001–06 of 88,935 people with depression and at least 2 antidepressant prescriptions,. The company took data for the health state costs from Unit Costs of Health and Social Care (2013) and NHS Reference Costs. The company assumed no treatments were prescribed to manage adverse reactions, but around one-third of people would incur an additional GP visit. Therefore, the company costed all adverse events based on an assumed 0.3 GP visits per patient per adverse reaction (£13.50).

5.10 To estimate health-related quality of life in the acute phase, the company used EQ-5D data from REVIVE (see table 8). However, for the maintenance phase, the company used EQ-5D data from Sapin et al. (2004). Sapin was a French study which enrolled 250 people with major

depressive disorder in primary care, and assessed health-related quality of life at baseline and after 8 weeks of treatment. The company noted that the mean MADRS score at baseline was 32.7 in Sapin compared with 29.1 in REVIVE, which may explain why the baseline EQ-5D score from Sapin was lower than the baseline EQ-5D score in REVIVE. The company included disutility values associated with adverse reactions from Sullivan et al. (2004), and applied them for 3 weeks in the company's base case analysis.

Table 8 Summary of utility values used in company's economic model (Table B59, page 168 of the company's submission)

Event	Utility value	Comment	Source
Acute phase (0-8 weeks)			
Depression (baseline)	0.54	None	REVIVE
Remission	0.85		
No remission	0.62	Weighted average of non-responders and responding non-remitters at 8 weeks	
Maintenance phase (after 8 weeks)			
Remission	0.85	EQ-5D score for 'responders remitters'	Sapin et al. 2004
Relapse/no remission	0.58	EQ-5D score for non-responders	
Recovery	0.85	Assumed equal to remission	
Disutility values of side-effects			
Sexual dysfunction	0.049	None	Sullivan et al. 2004
Headache	0.115		
Diarrhoea	0.044		
Somnolence	0.085	Assumed equal to drowsiness	
Nausea	0.065	Assumed average of gastrointestinal adverse reactions	
Insomnia	0.129	Assumed equal to anxiety	
Dry mouth	0.000	No data available, so company assumed no decrement	N/A
Dizziness	0.000		
Sweating	0.000		
Weight gain	0.032	Company calculation	Dixon et al. 2004 & REVIVE

ERG comments

5.11 The ERG highlighted that there was uncertainty around whether STAR*D was an appropriate study to inform the prognosis of people with depression whose condition had not remitted after first switching treatment. The ERG considered that STAR*D included treatments that did not reflect the comparators in the model, and that the population of STAR*D was different from the population of REVIVE. It explained that using data from STAR*D for subsequent switches imposes a poorer prognosis (that is, lower remission rates and higher relapse rates) than expected for a population with the same characteristics as in REVIVE. The ERG stated that using STAR*D may make the most effective initial switch treatment look even better (that is, vortioxetine in the company's base case analysis).

5.12 The ERG disagreed with the company's decision to use the same utility value for:

- relapse and
- people whose condition was not in remission after third or subsequent treatment

because they are very different health states. It highlighted that the utility value from Sapin et al (2004) used by the company for people whose condition had not achieved remission was lower than the utility value reported for people whose condition had not achieved remission at week 8 in the REVIVE trial. The ERG considered it was not necessary to use a different source for the utility values in the maintenance phase, and that using these 2 sources (REVIVE and Sapin et al. 2004) favoured vortioxetine in the company's base-case analysis. It also felt that the relapse health state should reflect the recurrence of moderate-to-severe major depression and so these people should return to their baseline level of utility (that is, 0.54). The ERG proposed alternative utility values for the company's model, see table 9.

Table 9 ERG's preferred utility values (Table 50, page 128 of the ERG report)

Health state	Company's utility	Company's source	ERG's utility	ERG's source
No remission (0-8 weeks)	0.62	REVIVE	0.67	REVIVE (FAS, MMRM): table 37, clarification letter
No remission (after 8 weeks)	0.58	Sapin (2004)	0.67	
Relapse (after 8 weeks)	0.58	Sapin (2004)	0.54	REVIVE (baseline depression)

5.13 The ERG commented that the company used the proprietary price of venlafaxine (extended-release form) rather than the generic price (immediate-release form). It also noted that the maintenance phase dose of citalopram used by the company exceeded the dose stated in its marketing authorisation.

5.14 The ERG stated that the parameter used reflecting the proportion of people stopping treatment because of adverse reactions had no impact on the cost-effectiveness estimates because the company assumed these people did not achieve remission. Because adverse reactions may differ between people who stop or who switch treatment, the ERG considered that the results are potentially biased.

Company's base-case results and sensitivity analysis

5.15 The company's deterministic cost-effectiveness results for vortioxetine compared with the comparators are presented in table 10.

Table 10 Company's base-case cost effectiveness results (Table B82, page 188 of company's submission)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Venlafaxine	£964	0.675	-	-	-
Vortioxetine	£971	0.694	£7	0.019	£378
Citalopram	£976	0.664	£5	-0.030	Dominated
Sertraline	£977	0.664	£0	-0.001	Dominated
Agomelatine	£1082	0.676	£105	0.012	Dominated

QALY, quality-adjusted life year.
Dominated, fewer QALYs at greater cost than comparator.

5.16 The company explored parameter and structural uncertainty in its economic model by presenting the results of 1-way sensitivity analyses, scenario analyses and a threshold analysis. The 1-way sensitivity analyses suggested the company's cost effectiveness results was most sensitive to:

- the difference in remission rates at 8 weeks (acute phase) between vortioxetine and each comparator
- GP consultation cost and the utility values for remission at 8 weeks and
- the relapse health state in the maintenance phase after 8 weeks.

However, in all but 2 of the company's 1-way sensitivity analyses vortioxetine remained dominant or had an ICER below £15,670 per QALY gained: vortioxetine was dominated by venlafaxine and by citalopram when including the lower bound of the 95% CI for the differences in remission rates at 8 weeks in the company's economic model. The company commented that its scenario analyses indicated that its economic model was robust to all of the structural assumptions and remained the most cost-effective treatment. Because the remission rate at 8 weeks was the most influential driver of the company's cost effectiveness results, it explored a threshold analysis around this parameter for vortioxetine, see table 11.

Table 11 Company's threshold analysis of remission rate for vortioxetine (Table B84, page 200 of company's submission)

Treatment	Remission rate at 8 weeks	£20,000 per QALY gained threshold	Remission at 8 weeks	£30,000 per QALY gained threshold
Vortioxetine (base case)	**40.50%**		**40.50%**	
Vortioxetine	30.53%		30.10%	
Venlafaxine	**33.30%**	£20,009	**33.30%**	£29,898
Vortioxetine	27.97%		28.54%	
Agomelatine	**29.50%**	£20,016*	**29.50%**	£29,973*
Vortioxetine	24.53%		24.00%	
Sertraline	**26.10%**	£20,075	**26.10%**	£30,062
Vortioxetine	24.10%		23.55%	
Citalopram	**23.70%**	£20,027	**23.70%**	£29,975

Figures in bold are base case remission rates.

* Threshold ICERs between vortioxetine and agomelatine are based on lower cost and fewer QALYs for vortioxetine, so the ICERs should be interpreted as willingness to accept QALYs lost, not willingness to pay for QALYs gained.

For further details around the company's sensitivity and scearnio analyses, see pages 176–83, 188–202 and Appendix 19 of the company's submission.

ERG comments

5.17 Given the issues highlighted by the ERG around the company's indirect treatment comparison (see sections 4.19 to 4.21), the ERG stated that there was considerable uncertainty associated with the ICERs. It concluded that the company's base case analysis can only be reliably used for comparisons of vortioxetine with agomelatine.

5.18 The ERG was aware from the World Health Organisation (2008) that an untreated major depressive episode lasts on average 5 to 6 months. The ERG calculated the average duration of a major depressive episode for each treatment included in the company's model based on approximating the mean number of months not spent in the remission and recovery health states. The ERG highlighted that the lowest estimated duration for

a major depressive episode for any given treatment in the company's model was for vortioxetine (6.73 months; longer than the 5 to 6 months stated by the World Health Organisation). The ERG explained that this assumes implicitly that people who switch treatment have a poorer prognosis compared with the broader major depressive disorder population, highlighting that therefore the trial populations used to inform the parameters for remission and relapse in the company's model are crucially important (for example, STAR*D; see section 5.11).

ERG exploratory analyses

5.19 The ERG presented deterministic ICERs for several exploratory analyses that used alternative sources of evidence for the relative effectiveness of vortioxetine compared with its comparators (see section 4.22 and table 12) and used the company's preferred utility values (see table 9).

- Exploratory analysis 1 (see table 13):
  - The dosage of treatment was up-titrated after 8 weeks (maintenance phase).
  - STAR*D used to inform remission and relapses rates for subsequent switchies after initial treatment.
- Exploratory analysis 2 (see table 14):
  - The same dosage of treatment for the acute and mainanteance phases rather than up-tritrated after 8 weeks.
  - STAR*D used to inform remission and relapses rates for subsequent switchies after initial treatment.
- Explortary analysis 3 (see table 15):
  - The dosage of treatment was up-titrated after 8 weeks.
  - Same rate of relapse applied for initial and subsequent switches rather than based on the the line of treatment (relapse rate taken from Limosin et al. 2004).
  - Assumed all treatments were equally effective for achieving remission at all stages of treatment (based on the average of the remission rates for the comparators at initial switch).

- Exploratory analysis 4 (see table 16):
  - The dosage of treatment was up-titrated after 8 weeks.
  - Same rate of relapse applied for initial and subsequent switches rather than based on the line of treatment (relapse rate taken from Limosin et al. 2004).
  - Assumed a decline in the effectiveness of each subsequent treatment (applying the proportionate reduction in effectiveness from STAR*D at each subsequent switch to average of the remission rates for the comparators at initial switch).

For further information around the ERG's exploratory analyses, see pages 126–39 of the ERG report.

Table 12 ERG's alternative scenarios for relative effectiveness: proportion of remitters at 8 weeks (Table 52, page 130 of the ERG report)

Treatment	Probability of remission			
	Company submission [from ITC]	***ERG scenario 1 [Llorca]***	***ERG scenario 2 [Pae]***	***ERG scenario 3 [equal effectiveness]***
Vortioxetine	40.50%	40.50%	40.50%	40.50%
Agomelatine	29.50%	35.81%	26.48%	40.50%
Sertraline	26.10%	--	--	--
Venlafaxine (XR)	33.30%	49.70%	42.52%	40.50%
Duloxetine	--	43.23%	49.30%	40.50%
Citalopram	23.70%	--	--	--
Escitalopram	--	40.74%	--	40.50%
ITC, indirect treatment comparison; XR, extended release.				

Table 13 ERG exploratory analysis 1 using STAR*D data [with up-titration] (Table 56, page 133 of the ERG report)

	Costs	QALYs	Incremental		ICER	
			Costs	QALYs	w SSRI	w/o SSRI
					(incremental analyses, in relation to next best)	
ERG scenario 1: Llorca et al. (2015)						
Venlafaxine (XR)	£885	0.736	ref	ref	ref	ref
Escitalopram	£887	0.729	£3	-0.007	Dominated	--
Vortioxetine	£971	0.733	£83	0.004	Dominated	Dominated
Duloxetine	£1,032	0.730	£61	-0.003	Dominated	Dominated

Agomelatine	£1,069	0.728	£36	-0.002	Dominated	Dominated
ERG scenario 2: Pae et al. (2014)						
Venlafaxine (XR)	£919	0.728	ref	ref	ref	NA
Vortioxetine	£971	0.733	£52	0.006	£9,191	NA
Duloxetine	£1,017	0.737	£46	0.003	£13,393	NA
Agomelatine	£1,088	0.717	£71	-0.020	Dominated	NA
ERG scenario 3: Equal effectiveness						
Escitalopram	£889	0.729	ref	ref	ref	--
Venlafaxine (XR)	£929	0.725	£40	-0.003	Dominated	ref
Vortioxetine	£971	0.733	£42	0.008	£18,188	£5,318
Duloxetine	£1,039	0.727	£68	-0.006	Dominated	Dominated
Agomelatine	£1,059	0.734	£20	0.007	£128,927	£128,927
ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year; SSRI, selective serotonin re-uptake inhibitor; XR, extended release; w, with; w/o, without.						

Table 14 ERG exploratory analysis 2 using STAR*D data [without up-titration] (Table 57, page 134–35 of the ERG report)

	Costs	**QALYs**	**Incremental**		**ICER**	
			Costs	**QALYs**	**w SSRI**	**w/o SSRI**
					(incremental analyses, in relation to next best)	
ERG scenario 1: Llorca et al. (2015)						
Venlafaxine (XR)	£869	0.736	ref	ref	ref	ref
Escitalopram	£886	0.729	£17	-0.007	Dominated	--
Vortioxetine	£971	0.733	£85	0.004	Dominated	Dominated
Duloxetine	£972	0.730	£1	-0.003	Dominated	Dominated
Agomelatine	£1,026	0.728	£54	-0.002	Dominated	Dominated
ERG scenario 2: Pae et al. (2014)						
Venlafaxine (XR)	£906	0.728	ref	ref	ref	NA
Duloxetine	£949	0.737	£42	0.009	£4,676	NA
Vortioxetine	£971	0.733	£22	-0.003	Dominated	NA
Agomelatine	£1,057	0.717	£86	-0.017	Dominated	NA
ERG scenario 3: Equal effectiveness						
Escitalopram	£887	0.729	ref	ref	ref	--
Venlafaxine (XR)	£917	0.725	£29	-0.003	Dominated	ref
Vortioxetine	£971	0.733	£54	0.008	£18,535	£6,899
Duloxetine	£983	0.727	£12	-0.006	Dominated	Dominated
Agomelatine	£1,010	0.734	£28	0.007	£57,955	£57,955
ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year; SSRI, selective serotonin re-uptake inhibitor; XR, extended release; w, with; w/o, without.						

Table 15 ERG exploratory analysis 3 assuming same relapse rate and average remission rate of 2nd line treatments [with up-titration] (Table 58, page 137 of the ERG report)

	Costs	QALYs	Incremental		ICER	
			Costs	QALYs	w SSRI	w/o SSRI
					(incremental analyses, in relation to next best)	
ERG scenario 1: Llorca et al. (2015)						
Escitalopram	£706	0.777	ref	ref	ref	--
Venlafaxine (XR)	£724	0.778	£17	0.001	£15,778	ref
Vortioxetine	£796	0.780	£72	0.002	£36,434	£36,434
Duloxetine	£856	0.777	£60	-0.003	Dominated	Dominated
Agomelatine	£882	0.778	£27	0.001	Dominated	Dominated
ERG scenario 2: Pae et al. (2014)						
Venlafaxine (XR)	£751	0.772	ref	ref	ref	NA
Vortioxetine	£806	0.778	£55	0.005	£10,394	NA
Duloxetine	£864	0.777	£58	-0.000	Dominated	NA
Agomelatine	£889	0.770	£25	-0.007	Dominated	NA
ERG scenario 3: Equal effectiveness						
Escitalopram	£713	0.775	ref	ref	ref	--
Venlafaxine (XR)	£752	0.772	£39	-0.003	Dominated	ref
Vortioxetine	£802	0.779	£50	0.006	£27,752	£7,882
Duloxetine	£862	0.774	£60	-0.005	Dominated	Dominated
Agomelatine	£891	0.779	£29	0.005	£196,655	£196,655
ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year; SSRI, selective serotonin re-uptake inhibitor; XR, extended release; w, with; w/o, without.						

Table 17 ERG exploratory analysis 4 assuming same relapse rate and average remission rate of 2nd line with proportionate reduction based on STAR*D [with up-titration] (Table 59, page 138 of the ERG report)

	Costs	QALYs	Incremental		ICER	
			Costs	QALYs	w SSRI	w/o SSRI
					(incremental analyses, in relation to next best)	
ERG scenario 1: Llorca et al. (2015)						
Escitalopram	£809	0.751	ref	ref	ref	--
Venlafaxine (XR)	£813	0.755	£3	0.005	£766	ref
Vortioxetine	£899	0.754	£86	-0.002	Dominated	Dominated
Duloxetine	£955	0.751	£56	-0.002	Dominated	Dominated
Agomelatine	£993	0.750	£38	-0.002	Dominated	Dominated
ERG scenario 2: Pae et al. (2014)						
Venlafaxine (XR)	£848	0.747	ref	ref	ref	NA
Vortioxetine	£906	0.752	£58	0.004	£13,068	NA

Duloxetine	£951	0.755	£45	0.003	£14,583	NA
Agomelatine	£1011	0.739	£60	-0.016	Dominated	NA
ERG scenario 3: Equal effectiveness						
Escitalopram	£815	0.749	ref	ref	ref	--
Venlafaxine (XR)	£854	0.746	£39	-0.003	Dominated	ref
Vortioxetine	£904	0.752	£50	0.006	£28,270	£7,992
Duloxetine	£964	0.748	£60	-0.005	Dominated	Dominated
Agomelatine	£993	0.753	£29	0.005	£200,797	£200,797
ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year; SSRI, selective serotonin re-uptake inhibitor; XR, extended release; w, with; w/o, without.						

Innovation

5.20 The company considered vortioxetine to be innovative because:

- it reduces cognitive dysfunction independent of its effect on MADRS (see section 5.1 of vortioxetine's SmPC)
- it has potential to minimise impact on social relationships (that is, strained family functioning through poorer communication, increased conflicts)
- it has potential to reduce symptoms associated with stopping treatment
- the health-related quality of life benefits may be underestimated (the EQ-5D instrument may not capture the impact of mental health conditions adequately compared with other diseases and conditions).

6 Equality issues

6.1 During the scoping workshop attendees indicated that there are equality issues with selective serotonin reuptake inhibitors for postmenopausal and elderly women, and discussed whether these subgroups would be affected by an appraisal of vortioxetine for major depressive disorder. The company indicated that vortioxetine is classed under 'other antidepressants', which makes it a "non-selective serotonin reuptake inhibitor". In addition, the clinical trials included adult men and women.

This issue relates to implementation and cannot be addressed through technology appraisal recommendations.

6.2 The company highlighted a report by the Royal College of Psychiatrists in its submission that noted “people with intellectual disability find it difficult to navigate through services and to negotiate the care they need. Therefore, it is essential that providers of services do not present barriers to their gaining access because of intellectual disability”.

This issue relates to implementation and cannot be addressed through technology appraisal recommendations.

7 Authors

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Appendix A: Clinical efficacy section of the European public assessment report

European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002717/WC500159447.pdf

"To summarise:

- Vortioxetine 1 mg/day was efficacious in the one study in which it was investigated.
- Vortioxetine 2.5 mg/day was not efficacious in either of the two studies in which it was investigated.
- Vortioxetine 5 mg/day was efficacious in five of the eight studies: the results were positive in four studies (two short-term studies in adult patients, the dedicated study in the elderly, and the relapse-prevention study) and supportive in a fifth study as reflected by additional sensitivity analyses in adult patients; no effect was observed in three short-term studies in adult patients.
- Vortioxetine 10 mg/day was efficacious in seven of the eight studies in which it was investigated: the results were positive in four studies (three short-term studies and the relapse-prevention study) and supportive in the remaining three studies as reflected by additional sensitivity analyses.
- Vortioxetine 15 mg/day was efficacious in one of the three studies in which it was investigated.
- Vortioxetine 20 mg/day was efficacious in all five studies in which it was investigated; the results were positive in four studies and supportive in one study.

It can therefore be concluded that the efficacy of vortioxetine was demonstrated with at least one dosage group across 9 of the 12 studies, showing at least a 2-point difference to placebo in the Montgomery and Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale 24-item (HAM-D24) total score. The clinical relevance of the effects were supported by the proportions of responders and remitters and the improvement in the Clinical Global Impression – Global Improvement (CGI-I) score. The efficacy of vortioxetine increased with increasing dose."

- *Conclusions on clinical efficacy, pages 122–23 of the EPAR*