Evidence Review Group Report

Vortioxetine for the treatment of major depressive disorder in adults [ID583]

Response to factual inaccuracy check

Issue 1

This is not a factual inaccuracy. The ERG report explicitly states that this is the opinion of the ERG.

No changes made.

Issue 2

This is not a factual inaccuracy. The ERG disagrees that statements have been used out of context.

No changes made.

Issue 3

p16: The text: “The manufacturer has criticised the use of active references”

Should read: “The EMA and the manufacturer have criticised the use of active references”

p142: The text: “The manufacturer has criticised the use of active references”

Should read: “The EMA and the manufacturer have criticised the use of active references”

At p14 results are deliberately presented without critique (which is given on p16). No changes made.

p74: The text: “however there is no evidence of such a bias in favour of venlafaxine.” should be deleted.

Issue 4

The ERG does not consider this to be a factual inaccuracy as it is an issue of how potentially biased data should be considered, however, for clarity, the following change should be made:

p74: The text: “particularly as there is a reasonably large number of such trials” should be deleted

Issue 5

p11: The text “but the review of indirect evidence”

Should read: “but, in the original MS, the review of indirect evidence”

p13: The text: “network meta-analysis were remission rate”

Should read: “network meta-analysis in the original MS were remission rate”

p38: The text: “The review of indirect evidence included significantly fewer outcomes”

Should read: “The review of indirect evidence presented in the original MS included significantly fewer outcomes”

p43: The text: “absolute changes in depression scores were included.”

Should read: “absolute changes in depression scores were included in the analysis in the original MS.”

p62: The text: “The indirect comparisons were performed for both remission rate”

Should read: “In the original MS, the indirect comparisons were performed for both remission rate”

Issue 6

These are not factual inaccuracies.

The ERG considers that the set of comparators included was too narrow as a consequence of the synthesis undertaken (these issues are discussed elsewhere in the ERG report).

The opinion of the ERG is that while a PSA was performed, there were several issues associated with the conduct and reporting of this:

- ICER results were given using the deterministic model, which gives an incorrect estimate in the case of a non-linear model.
- Additional issues: mean probabilistic inputs not equal to deterministic inputs, potential inconsistencies with parameters modelled as independent when should have been linked in some way.

Issue 7

The ERG considers that it is important to state the REVIVE was designed as a non-inferiority trial, and not a superiority trial, but accepts that there was evidence of superiority.

p15: The text: “but this result may not be reliable as this was a non-inferiority trial and was not powered to detect superiority of vortioxetine”

Should read: “The trial was designed as a non-inferiority trial, and was not designed to detect superiority of vortioxetine”

p45: The text: “Therefore any inferences from this trial regarding the superiority of vortioxetine over agomelatine may not be reliable as they may be based on chance.” should be deleted.

p58: The text: “conclusions regarding the superiority of vortioxetine versus agomelatine may not be reliable.”

Should read: “and was not designed to show superiority of vortioxetine.”

p79: The text: “but this result may not be reliable as this was a non-inferiority trial and was not powered to detect superiority of vortioxetine” should be deleted.

p141: The text: “but this result may not be reliable as this was a non-inferiority trial and was not powered to detect superiority of vortioxetine”

Should read: “The trial was designed as a non-inferiority trial, and was not designed to detect superiority of vortioxetine”

Issue 8

p15: The text: “agomelatine is not approved for use in the UK”

Should read: “agomelatine is not recommended for use by NICE”

p20: The text: “a drug not licenced in the UK”

Should read: “a drug not recommended for use by NICE”

p79: The text: “agomelatine is not approved for use in the UK”

Should read: “agomelatine is not recommended for use by NICE”

p145: The text: “a drug not licenced in the UK”

Should read: “a drug not recommended for use by NICE”

Issue 9

p12: The text: “On clarification the manufacturers also supplied adverse event data from 12 short-term placebo controlled trials of vortioxetine”

Should read: “Adverse event data from 12 short-term placebo controlled trials of vortioxetine were presented in an appendix and in the clarification response.”

p65: The text: “In response to this request the manufacturer provided data from 12 short-term placebo-controlled phase II/III studies, including one trial”

Should read: “Data from 12 short-term placebo-controlled phase II/III studies had been provided in an appendix to the MS, some of which was also provided in the clarification response. These trials included one trial”

Issue 10

p14 Table 3 and also p78 Table 26:

- For “(Standard error)”, read “(p-value)”
- For “Withdrawal” read “ Withdrawal due to AE”
- For “(0.470) **” read “(0.470)”

p14: The text: “and other antidepressants (except for agomelatine),”

Should read: “and other antidepressants,”

p78: The text: “The exception was that vortioxetine had a higher remission rate than agomelatine.” should be deleted.

Issue 11

p14: The text: “one regulatory submission”

Should read: “one HTA submission”

p14: The text: “and the regulatory submission”

Should read: “and the HTA submission”

p39: The text “submissions to regulatory authorities”

Should read: “submissions to regulatory or HTA authorities”

p72: The text: “submissions to regulators”

Should read: “submissions to regulatory or HTA authorities”

Issue 12

p15: The text: “The submission did not present any safety comparisons of vortioxetine with any active comparators”

Should read: “The submission did not present any safety comparisons of vortioxetine with any active comparators, other than as reported in the REVIVE and TAK318 trials”

Issue 13

This is not a factual inaccuracy, but for clarity the following should be changed:

p15: The text: “The ERG notes that this is a very narrow and specific population”

Should read: “The ERG notes that this is a very specific population”

Issue 14

This is not a factual inaccuracy, but for clarity the following should be changed:

p23: The text: “The submission recognises that the terms MDD and MDE are based on standard classifications from the Diagnostic and Statistical Manual of Mental Disorders (DSM); these are used to describe depression in the USA where terminology may differ slightly from that used in the UK, where the terms mild/moderate/severe depression are more commonly used.”

Should read: “The submission notes that the terms MDD and MDE are based on standard classifications from the Diagnostic and Statistical Manual of Mental Disorders (DSM). The terms MDE and MDD are used to describe depression in the USA; this terminology differs slightly from that used in the UK, where the terms mild/moderate/severe depression are more commonly used.”

Issue 15

This is not a factual inaccuracy, but the ERG is happy to clarify that some trials were healthy volunteer studies. The ERG considers it important to make clear that only a minority of trials have been in switch populations.

p27: The text: “Although vortioxetine has been studied in 24 completed trials involving over 7,000 patients”

Should read: “Although vortioxetine has been studied in 24 completed trials (some of which were healthy volunteer trials) involving over 7,000 patients”

Issue 16

This is not a factual inaccuracy.

No changes made.

Issue 17

The ERG has not been provided with an updated figure. Figure 6 on p51 should be replaced with the corrected version if possible. Otherwise, add a footnote to Figure 6 as follows:

“Erratum to figure: For PBO read Agomelatine; for VOR read Vortioxetine”

Issue 18

This is not a factual inaccuracy.

p52 Table 12: “(3.51 to -0.81)” should read: “(-3.51 to -0.81)”

Issue 19

The ERG notes that there appears to be some discrepancy across sources as how to define moderate depression based on HAM-D. The ERG accepts the citation provided as being up-to-date. The ERG considers there to be diversity in baseline HAM-D scores, even if all patients have at least moderate depression, so statements on pages 15 and 141 are not factually inaccurate.

p60: The text: “both have comparatively low baseline depression severity, below the standard threshold for moderate depression in the UK.”

Should read: “both have lower baseline depression severity than other trials.”

Issue 20

This is not a factual inaccuracy. The bias here refers to the inclusion of a potentially inferior treatment (agomelatine) at a critical point in the network.

No changes made.

Issue 21

p71: The text: “It may be less safe than agomelatine”

Should read “It may be less well tolerated than agomelatine”

Issue 22

p79: The text: “and five longer-term open label trials of vortioxetine”

Should read: “and five longer-term open label extension trials of vortioxetine”

Issue 23

Not a factual inaccuracy. The ERG notes that the fact that the evidence for duloxetine is based on potentially biased active reference arms is explicit elsewhere in the same section.

No changes made.

Issue 24

Not a factual inaccuracy. The analysis was based on hypothetical assumptions and hence the ERG did not consider that this analysis addressed uncertainties in the differential remission rates.

No changes made

Issue 25

Not a factual inaccuracy. The sentence continues in the following text (not in bold format). A formatting error was the reason for the separation of the text.

Bold text on page 107 should be in normal font, with no paragraph break between “the values in” and “table 34 had been…”.

Issue 26

P110: The text: “The manufacturer makes this assumption through observed increases in dosage from REVIVE”.

Should read: “The manufacturer makes this assumption through observed increases in dosage for each comparator from the respective trials included in the indirect treatment comparison”.

Issue 27

p130 Table 52: The text “45.52%”

Should read “42.52%”

Amended pages of the ERG report are presented below

The final NICE scope included a range of relevant outcomes, including response to treatment, remission, relapse, symptoms severity, anxiety, cognitive dysfunction, sleep quality, health-related quality of life and a range of adverse events. The manufacturer reported relevant data for most of these outcomes in the two trials of vortioxetine, but, in the original MS, the review of indirect evidence included only two outcomes (remission and withdrawal due to adverse events). This further limited the evidence on the relative efficacy, safety and cost-effectiveness of vortioxetine versus other active comparators.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The manufacturer's submission on clinical effectiveness included four systematic reviews: a review of RCTs of vortioxetine compared to active comparators in the switch population to evaluate efficacy; a review of non-RCT evidence of vortioxetine in the switch population; a review of adverse events of vortioxetine; and a review of indirect comparative evidence, again in the switch population, including an indirect treatment comparison and network meta-analysis of RCTs of other antidepressants, to evaluate efficacy and safety.

In response to the points for clarification, the manufacturer also provided meta-analyses of trials in the non-switch population.

1.2.1 Direct evidence in the switch population

As systematic review of RCTs of vortioxetine compared to active comparators in the switch population to evaluate efficacy was reported. It identified two trials, REVIVE and TAK318, summarised in Table 1. These trials were not combined in a meta-analysis because they were in different populations and used different comparators.

Table 1 RCTs included in the submission

Study	Regimen & duration	Comparator	Design	Follow-up duration	Primary outcome	Patient population
REVIVE (14178A)	Vortioxetine 10mg-20mg flexible dosing, 12 weeks	Agomelatine 25-50mg flexible dosing	Double-blind, international phase IIIb, parallel-group randomised trial	Efficacy: up to 12 weeks from baseline Safety: up to 16 weeks from baseline	Change from baseline in depression severity (MADRS total score) at week 8	Patients who have experienced an inadequate response to an SSRI or SNRI in their current MDE
TAK318	Vortioxetine 10mg-20mg flexible dosing, 8 weeks	Escitalopram 10-20mg flexible dosing	Double-blind, multicentre phase IIIb, parallel-group randomised trial	Efficacy: up to 8 weeks from baseline Safety: up to 12 weeks from baseline	Change from baseline in sexual functioning (CSFQ-14 total score) after 8 weeks of treatment	Patients who are well-controlled on an SSRI but experienced treatment emergent sexual dysfunction

MADRS: Montgomery and Åsberg Depression Rating Scale; CSFQ-14: Changes in Sexual Functioning Questionnaire Short-Form

The REVIVE trial was a well conducted trial comparing vortioxetine with agomelatine. The primary outcome in REVIVE was change in depression scores. Vortioxetine showed statistically significant superiority to agomelatine, reducing symptoms of depression. Average MADRS scores were 2.16 points lower on vortioxetine (95% CI 0.81 to 3.51) than on agomelatine after eight weeks. Vortioxetine was also superior to agomelatine in terms of response rate using MADRS at 8 weeks (OR 1.81, 95% CI 1.26 to 2.60) and remission rate (OR 1.72, 95% CI 1.17 to 2.52).

Vortioxetine and agomelatine had similar rates of treatment-emergent adverse events (around 54%) and serious adverse events (around 1.5%), but vortioxetine had lower rates of adverse events leading to withdrawal (5.9% vs 9.5%).

The TAK318 trial compared vortioxetine with escitalopram. The primary outcome was sexual functioning measured using the CSFQ-14 scale. At 8 week treatment the mean change from baseline was 8.8 (SE 0.64) in the vortioxetine arm and 6.6 (SE 0.64) in the escitalopram arm. This difference was statistically significant in favour of vortioxetine ($p = 0.013$). The submission also reported difference between arms on the CSFQ-14 subscales; there was statistically significant evidence in favour of vortioxetine on all subscales presented.

No differences between vortioxetine and escitalopram were identified for changes in depression scales, response, relapse or remission rates. Adverse event rates were similar on both treatments.

A systematic review for non-RCT evidence was performed, but no relevant studies were identified.

A systematic review for safety trials in the switch population was performed but no trials were identified. The search was expanded to the general, non-switch population and five open-label extensions of vortioxetine trials were identified.. Adverse event data from 12 short-term placebo controlled trials of vortioxetine were presented in an appendix and in the clarification response.

About 6% of patients had severe adverse events on vortioxetine compared to 4% on placebo in the placebo controlled trials. In the open-label extension trials 8.1% of patients had a serious adverse event. The manufacturer concluded that vortioxetine had a generally good safety profile. No data were submitted comparing adverse events using vortioxetine with other active treatments.

1.2.2 Indirect evidence in the switch population

The submission included a systematic review of treatments other than vortioxetine in the switch population used to perform an indirect treatment comparison with vortioxetine for efficacy and safety. This review identified seven trials. One was excluded on the grounds of poor trial quality. Two were placebo controlled trials not included in the primary network meta-analysis. Four trials were used in the primary network meta-analysis; there was only one trial included for each treatment comparison.

The outcomes of the network meta-analysis in the original MS were remission rate and withdrawal rate due to adverse events. A range of models were fitted using different assumptions, including the placebo controlled trials and using both frequentist and Bayesian statistical methods. A summary of the results from the main frequentist analysis are shown in Table 2. Results from other analyses were broadly consistent with these results.

Table 2 Summary of the results of the frequentist network meta-analyses

	Remission rate			Withdrawal rate due to adverse events		
	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

Vortioxetine had higher rates of remission than all other treatments, but results were only statistically significant for agomelatine. Vortioxetine also had lower rates of withdrawal due to adverse events than all other treatments, but results were only statistically significant for comparisons with sertraline, venlafaxine (XR) and bupropion. Due to the limited number of trials in the network, no assessments of heterogeneity or network inconsistency were performed.

1.2.3 Evidence syntheses of non-switch populations

As discussed in Section 1.1 the ERG questions the validity of restricting the analysis to switch populations. The ERG therefore requested that the manufacturer provide results from trials or meta-analyses of trials comparing vortioxetine to other active treatments and/or placebo in initial use and non-switch use populations. The manufacturer provided meta-analyses of their trials comparing

vortioxetine to placebo, but not for vortioxetine versus active comparators. The manufacturer also reported the existence of two submissions to regulators, four systematic reviews of vortioxetine trials and one indirect comparison of vortioxetine with other antidepressants.

The meta-analyses of trials submitted by the manufacturer and the four identified systematic reviews compared vortioxetine with placebo. There was considerable overlap in the trials included in the meta-analyses, and they reported different outcomes. However, all concluded that vortioxetine was superior to placebo.

Two systematic reviews and one HTA submission (to the Pharmaceutical Benefits Advisory Committee of Australia) compared vortioxetine to other antidepressants by using active reference arms from placebo controlled trials. Active reference arms are included in trials of antidepressants to ensure that patients are responding to therapy. An active reference should be a drug of proven superiority over placebo, so it can be used to check whether the trial has successfully treated patients by confirming a difference between the active reference and placebo. After reanalysis by the ERG of data from one of these reviews (Pae et al. 2014) vortioxetine was found to be inferior to duloxetine in terms of changes in depression scores, response rate and remission rate. There was no evidence of a difference between vortioxetine and venlafaxine. Results from the other review and the HTA submission were consistent with these results.

One systematic review (Llorca et al. 2015) performed an indirect comparison of vortioxetine with other antidepressants by analysing all placebo controlled trials of vortioxetine and other antidepressants. The results of the indirect treatment comparison are summarised in Table 3. This analysis found no statistically significant evidence of any difference in efficacy between vortioxetine and other antidepressants, but did find evidence that vortioxetine had a lower withdrawal rate due to adverse events than venlafaxine, desvenlafaxine and sertraline.

Table 3 Indirect treatment comparison by Llorca et al

	Results vs vortioxetine (p-value)						
	Agomelatine	**Desvenlafaxine**	**Duloxetine**	**Escitalopram**	**Sertraline**	**Venlafaxine**	**Vilazodone**
Efficacy at 2 months (SMD: <0 favours vortioxetine)	-0.156 (0.113)	0.025 (0.803)	0.090 (0.419)	-0.054 (0.695)	-0.037 (0.832)	0.124 (0.328)	-0.245 (0.111)
Withdrawal due to AE (Odds ratio: <1 favours vortioxetine)	1.769 (0.030) *	0.578 (0.035) *	0.752 (0.262)	0.671 (0.275)	0.299 (0.008) **	0.469 (0.009) **	0.640 (0.181)

Response rate (Odds ratio: >1 favours vortioxetine)	1.045 (0.815)	1.153 (0.364)	0.893 (0.514)	0.843 (0.523)	0.772 (0.575)	0.789 (0.353)	0.975 (0.934)
Remission rate (Odds ratio: >1 favours vortioxetine)	1.220 (0.470)	1.029 (0.852)	0.894 (0.526)	0.990 (0.981)	NA	0.689 (0.444)	0.983 (0.952)

** p-value 0.01 – 0.05; ** p-value <0.01*

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The restriction to a switch population meant that only two trials comparing the efficacy of vortioxetine with other antidepressants were submitted. The REVIVE trial comparing vortioxetine to agomelatine found vortioxetine had greater short-term reduction in depression scores and lower withdrawal rates due to adverse events. The trial was designed as a non-inferiority trial, and was not designed to detect superiority of vortioxetine. It should also be noted that agomelatine is not recommended for use by NICE as no evidence for its efficacy has been submitted. The TAK318 trial included patients who were switching due to sexual dysfunction but had responded to initial treatment. The ERG notes that this is a very specific population, so the TAK318 trial provided little information on the broader population who might take vortioxetine. It did find that vortioxetine reduced sexual dysfunction symptoms when compared to escitalopram. However it is not clear whether this finding is specific to vortioxetine, or whether any non-SSRI would have a similar beneficial effect. No efficacy evidence was submitted for the licensed 5mg vortioxetine dose.

Based on the safety evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. Most adverse were mild to moderate in intensity and there was no conclusive evidence that these were dose dependent. The submission did not present any safety comparisons of vortioxetine with any active comparators, other than as reported in the REVIVE and TAK318 trials, so the safety profile of vortioxetine compared to other antidepressants is uncertain.

The ERG has considerable concerns over the validity of the network analysis because of the high apparent diversity in the populations across trials, with very different included patients and severities of depression. For one trial (Kasper) the analysis used a subset of patients who had been treated in the year prior to enrolment. This is not the same as patients who were switching treatment, so the ERG does not think this trial should have been included. The ERG questions the validity of the indirect treatment comparison, but notes that the analysis found no convincing evidence of difference between vortioxetine and other treatments in terms of remission rate (except for agomelatine). There was some

evidence that vortioxetine may have lower withdrawal rates due to adverse events, but the high apparent heterogeneity across trials means the validity of this finding is questionable.

Given the limited nature of the data in the switch population the ERG considers that data in non-switching and initial-use populations should be considered. Although such data is not in the switch population it is relevant to the broader population of all patients with MDD specified in the NICE scope. The manufacturer justified excluding trials of non-switching populations by claiming that treatment efficacy in a switch population may be different from in initial use. The ERG considers that the evidence submitted to justify this claim is limited and refers only to patients who had previously used an SSRI, where switching to another SSRI may be less effective than a non-SSRI treatment. No evidence was presented to suggest that the relative efficacy of non-SSRIs may vary between initial and switch use, and no evidence was specific to vortioxetine. The ERG therefore concludes that this restriction was inappropriate and evidence on non-switch populations is relevant when examining the efficacy and safety of vortioxetine.

Direct evidence comparing vortioxetine to other active treatments in non-switching populations was only available from short-term placebo controlled trials with active reference arms. The EMA and the manufacturer have criticised the use of active references because they are not true randomised comparisons and patients known to be non-responsive to the reference are excluded, possibly biasing results in favour of the active reference. While the ERG accepts the potential for such bias it does not consider this potential bias to be substantial enough to exclude these trials. The ERG found no evidence of any difference in efficacy between vortioxetine and venlafaxine, based on two trials. There was evidence that vortioxetine was significantly inferior to duloxetine in terms of reducing depression scores, response and remission. While there is a possibility of bias in favour of duloxetine in these analyses it is not clear whether any bias would be sufficient to completely explain this inferiority.

An indirect treatment comparison in non-switch populations found no evidence of any difference in efficacy between vortioxetine and other treatments, but there was some evidence to suggest that vortioxetine had a lower withdrawal rate due to adverse events than some treatments, including sertraline and venlafaxine. While this is an indirect analysis, and not conducted in a switch population, the number of trials included in this analysis suggests that this may represent the most reliable evidence for comparing the efficacy and tolerability of vortioxetine to other treatments.

The ERG concludes, based on the totality of the evidence, that vortioxetine is likely to be of similar efficacy to other antidepressants, but may be superior to agomelatine and inferior to duloxetine. Vortioxetine appears to have a lower withdrawal rate due to adverse events than other treatments, and

2 Background

2.1 Critique of manufacturer's description of underlying health problem.

The manufacturer presents a suitable summary of major depressive disorder (MDD) and major depressive episodes (MDE) in manufacturer's submission (MS) sections 2.1 to 2.3; this includes their definition, progression over time, impact on health and quality of life and the impact and cost to the NHS and society in general.

The submission notes that the terms MDD and MDE are based on standard classifications from the Diagnostic and Statistical Manual of Mental Disorders (DSM). The terms MDE and MDD are used to describe depression in the USA; this terminology differs slightly from that used in the UK, where the terms mild/moderate/severe depression are more commonly used. The submission notes that MDD/MDE are approximately equivalent to moderate to severe depression as defined by NICE guidance.(1) An MDE is defined as the occurrence of depressed mood or a loss of interest or pleasure in life activities for at least two weeks, at least five of the nine core symptoms of depression and at least one significant impairment in social functioning (list provided in submission) occurring almost every day. Left untreated an MDE may last for two months to several years, but this may be greatly reduced by treatment.(2) The course of an MDE is characterised by five events: response, remission, recovery, relapse and recurrence,(3) as summarised in Figure 1. A patient whose symptoms improve sufficiently on treatment is considered to be responding, and is judged to be in remission when core symptoms of depression cease or are considered very minor. Patients remaining in remission for sufficient time are judged to have recovered. NICE recommends continuing treatment for at least six months following remission, and treatment may be continued for longer (two years or more) in cases of recurrent MDEs.(1) A patient may relapse at any time if symptoms worsen. If symptoms re-occur after recovery this is judged to be a recurrence and constitutes a new MDE. Relapse and lack of response are common, with approximately one-third to one half of patients not responding adequately to treatment,(4, 5) and at least half of all patients experiencing their first MDE will go on to have at least one more episode within the next ten years.(6)

The submission discusses the potential health impacts of depression, particularly the substantial loss of quality of life and potential reduction in life expectancy, including increased risk of suicide, and its impact on family members. The costs associated with depression are substantial, with 1.24 million people estimated to have depression in England, costing the NHS £1.68 billion, and averaging £2,805 per person.(7) The submission also noted the substantial wider economic cost of depression due to increased sick leave and absenteeism from work, and reduced productivity.

3 Critique of manufacturer's definition of decision problem

3.1 Population

The population described in the final NICE scope is adults with major depressive disorder, reflecting the licensed population. Vortioxetine has a marketing authorisation in the UK for the treatment of major depressive episodes in adults. However, the patient population considered by the manufacturer was restricted to a subset of the licensed patient population, namely:

"*adult patients with moderate-to-severe MDD who are experiencing an MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to alternative antidepressant*" (MS, p14).

The manufacturer cites the burden of initial treatment failure on patients, the health service and wider society to highlight the potential unmet clinical and economic need for more effective and better-tolerated options for patients requiring a switch of treatment where initial antidepressant treatment has failed. The manufacturer further justifies this restriction, stating that the distinct pharmacological profile and favourable tolerability profile of vortioxetine may be particularly suitable in the "switch population". This switch population is further defined by the manufacturer (MS, p38) as:

- *Patients who are experiencing a moderate-to-severe MDE, and*
- *whose current episode has been treated initially with an SSRI or SNRI, and*
- *who are candidates for a switch in the clinician's opinion, and*
- *who wish to change antidepressant treatment because of inadequate response or intolerability to the initial treatment.*

Although vortioxetine has been studied in 24 completed trials (some of which were healthy volunteer trials) involving over 7,000 patients, the manufacturer's submission focuses largely on 2 studies considered relevant to the decision problem; Study 14178A (REVIVE) and TAK318. These studies are subsequently used as the basis for short-term efficacy and tolerability data. Longer-term safety studies from a broader population including non-switch patients are also presented in the manufacturer's submission based on the assumption that tolerability and safety data are likely to be generalisable to a switch population. Based on clinical advice, the ERG considers this assumption to be appropriate for safety, but not for tolerability, as patients intolerant of one medication may be more intolerant of others.

The population considered within the manufacturer's submission is thus significantly restricted compared to the broader population stated in the final NICE scope and the licensed indication for vortioxetine. However, such a restriction is potentially consistent with the "Other considerations"

The review of indirect evidence presented in the original MS included significantly fewer outcomes, namely remission and withdrawal due to adverse events. The manufacturer stated that no other endpoints could be included in the review of indirect evidence as they were no reported consistently across all included studies. Although this justification appears appropriate, the absence of other outcomes (such as response rates) limits the relevance of the review of evidence comparing vortioxetine with several relevant comparators.

The MS cost-effectiveness model included some, but not all, of the effectiveness outcomes specified in the scope. In particular, the manufacturer did not include response data within the decision model.

3.5 Other relevant factors

The MS stated that no attempts were made to allow for equality considerations issues analytically, such as by applying alternative utility weightings. The MS noted that although people with intellectual disability are more likely to suffer from depressive episodes, this particular population may be at a disadvantage when it comes to receiving a specific diagnosis for depressive symptoms distinct from their other difficulties, and accessing the care they need (MS, Section 3, p.50). The ERG thinks that this approach was likely to be appropriate.

4 Clinical Effectiveness

The manufacturer submitted evidence on clinical effectiveness in the "switch" population based on four systematic reviews. This included three reviews of direct evidence for vortioxetine:

a) a review of RCTs of vortioxetine compared to active comparators in the switch population (MS, Sections 6.1 to 6.6) to evaluate efficacy;
b) a review of non-RCT evidence of vortioxetine in the switch population to evaluate efficacy (MS, Section 6.8);
c) a review of adverse events of vortioxetine (MS, Section 6.9).

Also submitted was a review of indirect comparative evidence, again in the switch population, including an indirect treatment comparison and network meta-analysis of antidepressant RCTs, to evaluate efficacy and safety (MS, Section 6.7).

Section 4.1 below summarises and critiques the methods of all four reviews. The first review identified two RCTs comparing vortioxetine to other active comparators, REVIVE and TAK318; these are critiqued in Section 4.2. The review of indirect treatment comparisons and its associated network meta-analysis are critiqued in Section 4.3. The review of non-RCT evidence did not identify any relevant studies, so this report does not consider this review in any detail (Section 4.4). The review of adverse events is critiqued in Section 4.5.

As discussed in Section 3 above, the ERG considers that the restriction to a switch population only is considerably narrower than the original scope specified and that assessment of the efficacy of vortioxetine should take account of the broader population by including evidence from studies of vortioxetine in non-switch populations. The ERG requested that the manufacturer provide data on all trials of vortioxetine compared to placebo and/or active comparators. The manufacturer supplied efficacy and adverse event data for their placebo controlled trials of vortioxetine. They also identified three published systematic reviews of vortioxetine, two submissions to regulatory or HTA authorities and one published indirect comparison of vortioxetine with other antidepressants, sponsored by the manufacturer. The ERG considers this evidence in the wider population to be of relevance when determining the clinical efficacy of vortioxetine; this evidence is critiqued in Section 4.6.

were used to pool the safety studies. The ERG notes that this method is not ideal as it ignores differences in populations and characteristics across studies.

Indirect treatment comparison

Trials included in the indirect treatment comparison were pooled using network meta-analysis methods. The submission used two different approaches: a frequentist analysis using the Boucher method and a Bayesian analysis performed using WinBUGS. The ERG recognises that both approaches are standard methods, and have been used appropriately in the submitted analyses.

The ERG has concerns with some of the methods used in the network meta-analysis. The primary outcome was remission rate. No other efficacy outcomes, such as response rate or absolute changes in depression scores were included in the analysis in the original MS. On clarification, the manufacturer stated that no other efficacy endpoint was consistently reported across all studies and hence they could not be included in the network meta-analysis. Remission was defined as a HAM-D score of seven or less, or a MADRS score of ten or less. Because different trials reported different depression scales these scales may not be exactly comparable, and some patients may have achieved remission on one scale but not another. Also, one trial (Kasper) did not report remission rates, so this was calculated from HAM-D scores, assuming scores followed either a normal or gamma distribution. Sensitivity analyses were performed to investigate the effect of using both these distributions, which was appropriate. However, remission rates may have been inaccurately estimated if the data did not fit either of these distributions. On clarification, the manufacturer presented results of a network meta-analysis with standardised mean difference in depression scale as the outcome.

The main network analysis excluded trials with a placebo arm. The manufacturer justified this based on clinical advice that patients in placebo-controlled studies may be different from those in active-controlled studies. No further justification was provided. The ERG does not consider this to be a strong justification, because such differences would apply to all placebo-controlled trials, and including such trials would be unlikely to bias the network analysis results as a whole. The manufacturer did provide results of the network including placebo-controlled trials in Appendix 16.

The MS reported results as risk differences between treatments. The ERG does not consider the risk difference to be a suitable measure for comparing treatments as is it very sensitive to any heterogeneity in outcomes across trials. The manufacturers justified this choice because using the risk difference led to more conservative estimates for venlafaxine, bupropion and citalopram. The ERG agrees that results were more conservative in this case, but considers results based on odds ratios or relative risks to be more statistically robust. The manufacturers provided results based on odds ratios in an appendix, and results for relative risks in response to requests for clarification.

limitations that may have affected their external validity. The ERG has particular concerns regarding the choice of comparator, duration of follow-up and study power.

Comparators

Agomelatine is not currently recommended by NICE. The fact that agomelatine is the only comparator in REVIVE means that, in the context of this appraisal, the relevance of this trial is limited. The use of escitalopram is also limited in UK patients experiencing SSRI-induced sexual dysfunction, which limits the relevance of TAK318 to current UK practice.

Follow-up duration

The 12-weeks follow-up duration of REVIVE is short considering the duration of treatment that is recommended by NICE to achieve and consolidate remission. The manufacturer acknowledged this limitation (MS, p.136), but stated that this shortcoming was mitigated by the results of a relapse-prevention trial (study 11985A)(14) that found significantly lower relapse rates for vortioxetine compared with placebo (13% versus 26%, p=0.0013), over 24 weeks after 12 weeks' open-label treatment. The results of study 11985A should be interpreted with caution as it only included patients who were in remission at 10 and 12 weeks of open-label vortioxetine therapy, and therefore excluded responders-only, or patients who may have been in remission following a longer course of therapy. As with REVIVE, TAK318 had a short-term follow-up, therefore evidence of long-term efficacy of vortioxetine in switch populations is uncertain.

Study power

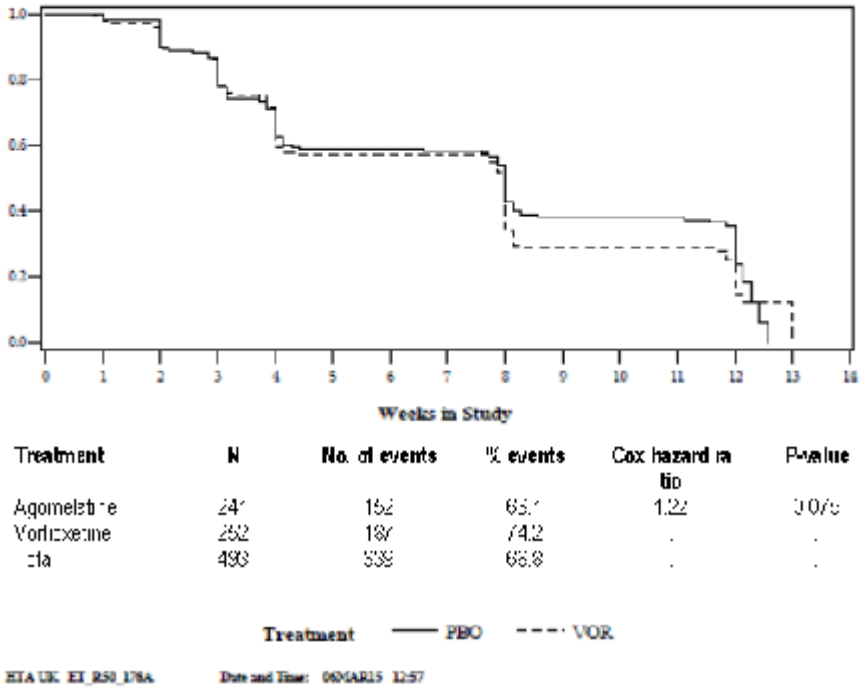
REVIVE was designed as a non-inferiority trial. Sample size calculations were based on a non-inferiority comparison of the treatment groups in the primary outcome, and non-inferiority was considered established if the upper bound of the two-sided 95% confidence interval of the difference between treatment groups in MADRS total score at Week 8 did not exceed 2 MADRS units compared with agomelatine. This means that REVIVE may not have been sufficiently powered to demonstrate that vortioxetine is superior to agomelatine.

Additional concerns about the representativeness of the trial populations are reported in sections 4.2.3 (REVIVE) and 4.2.5 (TAK318) of this report.

4.2.2 Quality assessment and risk of bias

The manufacturer provided a quality assessment of the two included trials of vortioxetine (REVIVE and TAK318) in MS section 6.4, Tables B11 and B12 (MS, pp. 83-87). These are summarised in Table 9 below. The ERG mostly concurs with the manufacturer's assessment of quality for the two

Figure 6 Kaplan Meir plot of time to first response (50% reduction in MADRS)



Treatment	N	No. of events	% events	Cox hazard ratio	P-value
Agomelatine	247	162	65.7	1.22	0.075
Vortioxetine	252	187	74.2	.	.
Total	499	339	69.8	.	.

Erratum to figure: For PBO read Agomelatine; for VOR read Vortioxetine

The results of this analysis showed a small separation between groups in favour of vortioxetine from 8 weeks, although the time-to-event analysis yielded a non-statistically significant result (p=0.075). This analysis should be interpreted with caution as it reports time to first response, and does not take into account patients who may have responded at early assessments but did not maintain response until the end of the study, as acknowledged by the manufacturer.

Severity of depression

Table 12 below presents differences in mean change from baseline between vortioxetine and agomelatine and shows that efficacy results were statistically significant across MADRS, CGI-S and CGI-I scores at treatment weeks eight and 12. REVIVE reported a reduction of 16.5 MADRS points (from 29.1 at baseline) in the vortioxetine group, and a reduction of 14.4 points (from 28.66 at baseline) in the agomelatine group, giving a mean difference of -2.16 (95% CI -3.51 to -0.81). The manufacturer stated that non-inferiority was established, as the upper bound of the 95% CI was below the non-inferiority margin of +2 MADRS points versus agomelatine. The magnitude of the results

Based on the TAK318 trial results, the manufacturer stated that vortioxetine is superior to escitalopram in improving sexual functioning in patients with SSRI-induced sexual dysfunction. They stated that both vortioxetine and escitalopram maintained and slightly improved the depressive symptoms seen with the prior SSRI treatment as assessed by MADRS, CGI-S, and CGI-I scores, and that vortioxetine was generally well-tolerated in this study.

REVIVE and TAK318 trials appeared well conducted. However, the designs of both studies raised a number of concerns. As mentioned above (Section 4.2.1), both trials included comparators of limited relevance to UK practice, and there were concerns about the representativeness of the trial participants to the UK switch population. Both studies had short-term follow-up, therefore the long-term efficacy of vortioxetine in switch patients is uncertain based on the evidence presented. In addition, the trials only evaluated the efficacy of vortioxetine 10-20mg/day, therefore the efficacy of the licensed 5mg/day regimen is uncertain. Finally, as REVIVE was designed as a non-inferiority trial, and was not designed to show superiority of vortioxetine.

4.3 Indirect treatment comparison

4.3.1 Critique of trials identified and included in the indirect comparison

The systematic review for the indirect comparison analysis identified 27 relevant studies; however 20 were excluded as not being in "switch" populations. The ERG accepts that these studies did not meet the inclusion criteria for the manufacturer's analysis, but many of these studies may have matched the NICE scope population of adults with MDD.

The seven remaining studies were assessed for study quality. For five studies, all quality components were assessed as either adequate or unclear. One study (Rush 2006(5)) had one component (imbalances between groups) considered to be inadequate. The ERG generally agrees with the manufacturer on their quality assessment of these trials.

One study (Rosso 2012(15)) had two inadequate components (randomisation and blinding). Given the high potential for bias in this trial it was excluded from further analysis. The ERG accepts that assessment of bias was correct and so this exclusion was reasonable, but notes that, as Rosso 2012 was the only study to include duloxetine, this means no evidence comparing vortioxetine to duloxetine has been presented.

the trials. In particular the withdrawal rates on venlafaxine (XR) and citalopram were around 18% in the model (Table 17) but only around 5% in the Lenox-Smith trial (Table 16).

4.3.3 Conclusions of the indirect treatment comparison

The manufacturer concluded that the network meta-analysis showed that vortioxetine is more efficacious and better tolerated than a range of comparator antidepressants.

The ERG does not concur with this conclusion for a variety of reasons. Wide confidence intervals mean that there was little evidence of a statistically significant improvement in efficacy with vortioxetine compared to other treatments. The network meta-analysis used in the indirect treatment comparison was limited to only four trials. Removing any trial would leave the network unconnected. The ERG has concerns as to whether the Kasper trial should have been included as the subgroup analysis used from this trial was not specifically of a switch population.

There is also evidence of substantial heterogeneity in the populations included across the trial, for example in the severity of depression, and apparent heterogeneity in the results of each trial. The limited number of trials meant that formal assessments of heterogeneity and network inconsistency could not be performed. Given these concerns the ERG concludes that the indirect treatment comparison reported in the submission does not provide valid evidence form which any conclusion on the efficacy of vortioxetine may reasonably be drawn.

4.4 Non-RCT evidence

The manufacturers performed a search for evidence other than RCTs but did not identify any relevant studies. The ERG did not find any evidence that relevant non-RCT studies of efficacy in switch patients had been missed.

4.5 Adverse events

The manufacturer performed a search for safety trials of vortioxetine in the "switch" population. None were identified so the search was widened to include all safety trials of vortioxetine. This search identified six studies, of which five were one-year open-label extensions of short-term efficacy trials and were eligible for inclusion in a pooled analysis. This pool included a total of 2,587 patients who continued from short-term, randomised placebo controlled trials and received flexible doses of vortioxetine 2.5 to 20mg/day.

Given that the manufacturer had broadened the scope in the search for adverse event data to all vortioxetine trials, the ERG requested the manufacturer supply adverse event data from all placebo or active control trials they had performed. Data from 12 short-term placebo-controlled phase II/III studies had been provided in an appendix to the MS, some of which was also provided in the

clarification response. These trials included one trial (12541A) that was conducted in patients aged over 65 years. This short-term pool included a total of 3,904 patients treated with vortioxetine.

Table 20 provides a list of studies included in the two pools, and is presented below. None of the studies included were conducted in switch populations. Further details of the pools are presented below.

Table 20 Overview of pools for the evaluation of the safety and tolerability of vortioxetine

Pool	Number of studies included	Study ID
Short-term placebo controlled pool	12	11492A , 11984A, 305, 13267A, 315, 316, 14122A, CCT-002, 303, 304, and 317, and 12541A
Open-label long-term pool	5	11492C, 11984B, 301, 13267B, and 314

4.5.1 Short-term pool of placebo controlled studies

The results of the review of long-term continuation studies of adverse events were reported in a separate document(23) and summarised in clarifications. A summary of incidence of TEAE during the core treatment period (from first dose to last dose in the double-blind treatment period) for vortioxetine and placebo is presented in Table 21 below. The manufacturer stated that the 15mg dose will not available in the UK, but results for this regimen were presented here for the sake of completion.

The overall incidence of TEAEs was 64.2% in the vortioxetine group, and 57.9% in the placebo group. The Treatment-emergent adverse event (TEAE) with the highest incidence in all the active treatment groups was nausea. The incidence of nausea was 8.1% in the placebo group and 24.1% in the total vortioxetine group (relative risk 3.02; 95% CI 2.57 to 3.55). Headache, which was the TEAE with the highest incidence in the placebo group, had similar incidences in all the treatment groups (approximately 13%).

For the majority of the patients with TEAEs, the TEAEs were mild or moderate. The incidence of severe TEAEs was similar in the placebo group and in the vortioxetine total group (4.4% and 5.5%, respectively). In the vortioxetine dose groups, the incidence of severe TEAEs ranged from 4.1% in the 20mg group to 7.0% in the 5mg group.

The overall incidence of TEAE leading to withdrawal in the vortioxetine total group was higher in the vortioxetine group (6.0%) compared with placebo (4.0%), and higher in 15-20mg doses compared with 5-10mg doses (4.8% [5mg], 5.8% [10mg], 8.0% [15mg], and 7.0% [20mg]). The most common

4.5.2.1 Conclusions of the review of safety studies

No separate conclusions were provided for the review of safety studies, although the manufacturer stated that vortioxetine had a favourable safety profile in an overview of safety in relation to the decision problem (section 6.9.3).

The ERG agrees that based on the evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. The analysis of the pooled placebo controlled trials and the analysis of the pooled continuation studies included relatively large patient numbers and showed broadly comparable results. Although the incidence of adverse events was high in patients receiving vortioxetine, most AEs were mild to moderate in intensity and there was no conclusive evidence that these were dose-dependent.

However, both pooled analyses had limitations. All analyses from the pool of continuation studies were uncontrolled, and as such they are at high risk of confounding (notably due to the placebo effect). All continuation studies were one-year extensions, and nearly half of patients received vortioxetine for less than one year, which is significantly less than for patients for whom maintenance may be recommended for two years or more. Some relevant studies may have been missed, since only studies that reported safety as a primary outcome were included. Results from the pool of placebo-controlled studies showed that the rate of patients with adverse events was high for vortioxetine (64.2%) as well as for placebo (57.9%), indicating a high placebo effect, although there was a statistically significant higher risk in the incidence of some specific adverse events, particularly nausea and vomiting (approximately 3 and 3.5 times higher than placebo). These results are in line with those of the Pae 2014 review(24), which found that nausea and vomiting were some of the most common AEs reported, and had an incidence that was significantly higher in the vortioxetine than in the placebo group. They also found that nausea was the single most common AE reported as a reason for discontinuation of vortioxetine, and found that its frequency showed a trend toward a dose–response relationship. Compared with placebo, withdrawal due to adverse events was slightly higher for vortioxetine, particularly in higher treatment doses (15-20mg).

The MS and clarifications presented no evidence of adverse events when comparing vortioxetine with active comparators. The ERG concludes that the best data available are that from the two trials (REVIVE, TAK318) discussed above in Section 4.2. The indirect treatment comparisons provided by the manufacturer and in Llorca et al(22) both reported withdrawal due to adverse events, which can be considered a reasonable proxy for adverse events overall. These results are discussed in sections 4.3 and 4.6. Based on these results there is some evidence that vortioxetine has a better adverse event profile than other drugs, including venlafaxine and duloxetine. It may be less well tolerated than agomelatine, although this conflicts with results from REVIVE.

4.6 Evidence syntheses of non-switch populations

As discussed in Section 3 the ERG questions the validity of restricting the analysis to "switch" populations. The evidence to suggest that there is a difference in treatment efficacy between initial use and switch use is limited,(1, 11) and restricted to showing that where patients are switching from an SSRI due to lack of response or intolerance, a non-SSRI may be more effective than another SSRI in these switching patients.(25) There is no evidence currently available to suggest that the relative efficacy of non-SSRIs differs between initial-use and switch populations. The ERG thinks that initial-use trials should be considered as providing relevant supporting evidence, particularly for the relative efficacy of non-SSRIs, given the limited nature of the evidence in the switch population identified by the manufacturer.

The ERG therefore requested that the manufacturer provide results from trials or meta-analyses of trials comparing vortioxetine to other active treatments and/or placebo in initial use and non-switch use populations.

In response the manufacturer:

1. Provided their own meta-analyses of trials comparing vortioxetine to placebo.
2. Reported the existence of two submissions to regulatory or HTA authorities:
   - Pharmaceutical Benefits Advisory Committee (PBAC, Australia)(26)
   - Canadian Agency for Drugs and Technologies in Health (CADTH)

   However, they did not provide these submissions; a redacted version of the PBAC report is in the public domain but the CADTH report has not been made public.

3. Identified four systematic reviews of vortioxetine:
   - Pae et al 2014(24)
   - Berhan and Barker 2014(27)
   - Citrome 2014(28)
   - Meeker et al 2015(29) (this review was published very recently and so was identified by the manufacturer subsequent to the MS and response to clarifications)
4. Identified one indirect treatment comparison sponsored by the manufacturer (Llorca 2015).(22)

The ERG thinks that all these analyses in non-switch populations provide relevant evidence on the efficacy of vortioxetine, and considers this evidence below.

4.6.1 Vortioxetine vs placebo

4.6.2 Vortioxetine vs active comparators

The submission to PBAC, the Pae and Meeker meta-analyses all considered trials comparing vortioxetine to an active comparator. The trials included in these analyses were generally placebo controlled trials with an active reference arm, except for one randomised trial evaluating vortioxetine and venlafaxine in a head-to-head comparison which was included in the submission to PBAC.(30) In the original submission, the manufacturer criticised the use of these active references arms (MS, Sections 1.4.1 and 2.8.2). Active reference arms are included in trials of antidepressants to ensure that patients are responding to therapy. An active reference should be a drug of proven superiority over placebo, so it can be used to check whether the trial has successfully treated patients by confirming a difference between the active reference and placebo. Patients known to be non-responders to the active reference are excluded from this arm, so the active reference arm may include patients more likely to respond to treatment. The manufacturer therefore claimed that any comparison of vortioxetine with an active reference may be biased towards the active reference.

The ERG recognises the potential for bias because the comparison between vortioxetine and active reference is not truly randomised and there is the potential for patients to differ in likely response to treatment between arms. However, the ERG does not consider this risk of bias to be sufficiently substantial to reject such comparisons altogether. The results of these comparisons discussed in the Pae and Meeker analyses, and the PBAC submission are therefore considered below.

4.6.2.1 Pae et al.

In Pae et al. meta-analyses comparing vortioxetine to active comparator for standardised mean difference, response and remission rates were presented. The analysis did not distinguish between the different comparator treatments. Based on the references in the paper the ERG has reanalysed the data, grouping trials by the comparator included in each trial.

Figure 10 shows the results based on data from the trials in the Pae meta-analysis for standardised mean difference in depression score between arms. Figure 11 shows the results for response rate, and Figure 12 for remission rate. In all three cases vortioxetine is superior to agomelatine based on the trial of Dragheim.(31) This trial appears to be an early presentation of the results of the REVIVE trial, but this could not be confirmed because the trial was reported only as a conference presentation which the ERG could not access. There is no evidence of a difference between vortioxetine and venlafaxine, based on one trial. Vortioxetine is consistently and statistically significantly inferior to duloxetine for all three outcomes. The potential that results were biased in favour of duloxetine given the potential for bias discussed above must be considered.

Figure 10 Forest plot of standardised mean difference based on data from Pae et al.

Table 26 Indirect treatment comparison by Llorca et al.

Outcome	Results vs vortioxetine (p-value)						
	Agomelatine	Desvenlafaxine	Duloxetine	Escitalopram	Sertraline	Venlafaxine	Vilazodone
Efficacy at 2 months (SMD: <0 favours vortioxetine)	-0.156 (0.113)	0.025 (0.803)	0.090 (0.419)	-0.054 (0.695)	-0.037 (0.832)	0.124 (0.328)	-0.245 (0.111)
Withdrawal due to AE (Odds ratio: <1 favours vortioxetine)	1.769 (0.030) *	0.578 (0.035) *	0.752 (0.262)	0.671 (0.275)	0.299 (0.008) **	0.469 (0.009) **	0.640 (0.181)
Response rate (Odds ratio: >1 favours vortioxetine)	1.045 (0.815)	1.153 (0.364)	0.893 (0.514)	0.843 (0.523)	0.772 (0.575)	0.789 (0.353)	0.975 (0.934)
Remission rate (Odds ratio: >1 favours vortioxetine)	1.220 (0.470)	1.029 (0.852)	0.894 (0.526)	0.990 (0.981)	NA	0.689 (0.444)	0.983 (0.952)

** p-value 0.01 – 0.05; ** p-value <0.01*

This analysis generally found no statistically significant evidence of a difference in efficacy between vortioxetine and any other treatment. Vortioxetine generally had a lower withdrawal rate than other treatments, although the results were only statistically significant for desvenlafaxine, sertraline and venlafaxine. Agomelatine had a lower withdrawal rate than vortioxetine.

This analysis was not performed in a "switch" population, however the findings of this analysis are consistent with those from the indirect treatment comparison in the switch population submitted by the manufacturer (except for agomelatine and withdrawal).

4.7 Conclusions of the clinical effectiveness section

The manufacturer's submission focused on trials in patients who had previously received antidepressants for a current MDE but were switching treatment to vortioxetine due to lack of response or adverse events; the "switch" population. As discussed in Section 3The ERG notes that this is a substantial restriction when compared to the original scope, which specified a general population of all adults with MDD.

The restriction to a switch population meant that only two trials comparing the efficacy vortioxetine with other antidepressants were submitted. Both trials were generally well conducted but there were a number of issues related to their design and their population which may limit the applicability of their results to UK practice. The REVIVE trial comparing vortioxetine to agomelatine found vortioxetine

had greater reduction in depression scores and lower withdrawal rates due to adverse events. It should also be noted that agomelatine is not recommended for use by NICE as no evidence for its efficacy has been submitted.

The TAK318 trial included patients who were switching due to sexual dysfunction but had responded to initial treatment. The ERG notes that this is a very narrow and specific population, so the TAK318 trial provided little information on the broader population who might take vortioxetine. It did find that vortioxetine reduced sexual dysfunction symptoms when compared to escitalopram. However it is not clear whether this finding is specific to vortioxetine, or whether any non-SSRI would have a similar beneficial effect.

The restriction to switch populations meant that the indirect treatment comparison in the submission included only four trials in its main analysis. The ERG has considerable concerns over the validity of the network analysis because of the high apparent diversity in the populations across trials, including very different patients and severities of depression. For one trial (Kasper) the analysis used a subset of patients who had been treated in the past year. This is not the same as patients who were switching treatment, so the ERG does not think this trial should have been included; without it, there is no connected network, rendering the analysis invalid. As such the ERG does not think the results of the indirect treatment comparison are valid, but notes that the analysis found no convincing evidence of difference between vortioxetine and other treatments in terms of remission rate (except for agomelatine). There was some evidence that vortioxetine may have lower withdrawal rates, but the high apparent heterogeneity across trials means the validity of this finding is questionable.

The manufacturers did not identify any trials reporting safety data in the switch population other that data reported in REVIVE and TAK318. The manufacturers therefore expanded the review of safety data to non-switch populations. This review identified 12 short-term placebo controlled trials and five longer-term open label extension trials of vortioxetine. In the placebo controlled trials severe adverse event rates and adverse events leading to withdrawal were more common on vortioxetine than placebo. However, based on the evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. Both the analysis of placebo controlled trials and the analysis of continuation studies included relatively large patient numbers and showed broadly comparable results. Although the incidence of adverse events was high in patients receiving vortioxetine, most AEs were mild to moderate in intensity and there was no conclusive evidence that these were dose-dependent. The manufacturer did not present any safety comparisons of vortioxetine with any active comparators in the broad MDD population, so the safety profile of vortioxetine compared to other antidepressants is uncertain.

Importantly, too, costs are assumed to be different in the acute phase compared to the remainder of the 12 months.

5.3.9.2 Acquisition costs

The acquisition costs for antidepressants are based upon the cheapest way of achieving the required daily dose, which in the acute phase is given by the WHO DDD (defined daily dose). In the case of agomelatine, an additional cost is factored in, which is the cost of carrying out a liver function test. In the acute phase, it is assumed that three liver function tests will be administered for each patient.

Table 39 Acute phase drug acquisition costs

Treatment	Assumed pack	Pack price	Dose in acute phase	Additional cost	Daily cost in acute phase
Vortioxetine	28 x 10mg Brintellix	£27.72	10mg	n/a	£0.99
Agomelatine	28 x 25mg Valdoxan	£30.00	25mg	3 x liver function test	£1.46
Sertraline	28 x 50mg	£1.75	50mg	n/a	£0.06
Venlafaxine	28 x 150mg VenlaBlue XR	£9.95	100mg	n/a	£0.24
Citalopram	28 x 20mg	£1.10	20mg	n/a	£0.04

Pack prices are taken from MIMS December 2014. Because doses are routinely adjusted upwards following initial treatment, the decision model allows for a higher dosage in the maintenance phase compared to that assumed in the acute phase. The manufacturer makes this assumption through observed increases in dosage for each comparator from the respective trials included in the indirect treatment comparison. In reality doses may be up-titrated at various points, for example after 2-4 weeks, but in the model the dose is raised after 8 weeks only. The results of dose titration for acquisition costs are illustrated in the table below.

Table 40 Post-acute phase drug acquisition costs

Treatment	Assumed pack	Pack price	Dose in maintenance phase	Additional cost	Daily cost in acute phase
Vortioxetine	28 x 20mg Brintellix	£27.72	20mg	n/a	£0.99
Agomelatine	28 x 25mg Valdoxan	£30.00	42.93mg	2 x liver function test per 8 weeks	£2.10
Sertraline	28 x 50mg	£2.15	135.5mg	n/a	£0.10
Venlafaxine	28 x 150mg VenlaBlue XR	£9.95	192.3mg	n/a	£0.46
Citalopram	28 x 40mg	£1.28	51mg	n/a	£0.06

8 Overall conclusions

8.1 Clinical effectiveness

The manufacturer restricted consideration of vortioxetine to patients who were switching from an initial antidepressant because the initial therapy was ineffective or not tolerated. This "switch" population is considerably narrower than the broad population specified in the scope

The restriction to a switch population meant that only two trials directly comparing the efficacy vortioxetine with other antidepressants were included in the MS. The REVIVE trial comparing vortioxetine to agomelatine found vortioxetine had greater reduction in depression scores and lower withdrawal rates due to adverse events. The trial was designed as a non-inferiority trial, and was not designed to detect superiority of vortioxetine. It should also be noted that agomelatine is not approved for use in the UK as no evidence for its efficacy has been submitted to NICE. The TAK318 trial included patients who were switching due to sexual dysfunction but had responded to initial treatment. The trial found that vortioxetine reduced sexual dysfunction symptoms when compared to escitalopram. The ERG notes that this is a very narrow and specific population, so the TAK318 trial provided little information on the broader population who might take vortioxetine.

The ERG has considerable concerns over the validity of the network analysis because of the high apparent diversity in the populations across trials, with very different included patients and severities of depression. The ERG does not think the results of the indirect treatment comparison are valid, but notes that the analysis found no convincing evidence of a difference between vortioxetine and other treatments in terms of remission rate (except for agomelatine). There was some evidence that vortioxetine may have lower withdrawal rates, but the high apparent heterogeneity across trials means the validity of this finding is questionable.

Based on the safety evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. Most adverse events were mild to moderate in intensity and there was no conclusive evidence that these were dose-dependent. The submission did not present any safety comparisons of vortioxetine with any active comparators, so the safety profile of vortioxetine compared to other antidepressants is uncertain.

Given the limited nature of the data in the switch population the ERG considers that data in non-switching and initial-use populations should be considered. Although such data are not in the switch population it is relevant to the broader population of all patients with MDD specified in the NICE scope. The manufacturer justified excluding trials of non-switching populations by claiming that treatment efficacy in a switch population may be different from in initial use. The ERG considers that the evidence submitted to justify this claim was limited. The ERG therefore concludes that this

restriction was inappropriate and evidence on non-switch populations is relevant when examining the efficacy and safety of vortioxetine.

Direct evidence comparing vortioxetine to other active treatments in non-switching populations was primarily available from placebo controlled trials with active reference arms. The EMA and the manufacturer have criticised the use of active references because they are not true randomised comparisons and patients known to be non-responsive to the reference are excluded, possibly biasing results in favour of the active reference. While the ERG accepts the potential for such bias it does not consider this potential bias to be substantial enough to exclude these trials. The ERG reanalysed results from these trials and found no evidence of any difference in efficacy between vortioxetine and venlafaxine, based on two trials. There was evidence that vortioxetine was inferior to duloxetine in terms of reducing depression scores, response and remission. While there is a possibility of bias in favour of duloxetine in these analyses it is not clear whether any bias would be sufficient to completely explain this inferiority.

An indirect treatment comparison in non-switch populations found no evidence of any difference in efficacy between vortioxetine and other treatments, but there was some evidence to suggest that vortioxetine had a lower withdrawal rate due to adverse events than some treatments, including sertraline and venlafaxine. While this is an indirect analysis, and not conducted in a switch population, the number of trials included in this analysis suggests that this may represent the most reliable evidence for comparing vortioxetine to other treatments.

The ERG concludes, based on the totality of the evidence, that vortioxetine is likely to be of similar efficacy to other antidepressants, but may be superior to agomelatine and inferior to duloxetine. Vortioxetine appears to have a lower withdrawal rate due to adverse events than other treatments, and so may have a better overall safety profile, however data on adverse events with vortioxetine, particularly when compared to other antidepressants, are too limited to draw any firm conclusions on the safety of vortioxetine.

8.2 Cost effectiveness

The MS presents cost-effectiveness evidence for vortioxetine as a second line option for MDE ("switch population"), a restriction to its licensed indication and the scope of the NICE appraisal. The ERG considers that the appropriate population and potential position of vortioxetine within current pathways should have been more formally considered by the manufacturer.

The MS establishes cost-effectiveness assuming the use of vortioxetine in primary care. The MS presents a decision model that evaluates the progression of a single MDE. The model is based on

treatment. No evidence was presented to suggest that the relative efficacy of non-SSRIs may vary between initial and switch use, and no evidence was specific to vortioxetine.

This restriction also meant that only two trials comparing vortioxetine to other antidepressants were presented. One compared vortioxetine to a drug not recommended for use by NICE, and the other was focused only on patients with SSRI treatment-emergent sexual dysfunction. Therefore neither appeared representative of most UK patients likely to be switching antidepressant treatments.

The restriction meant than only four trials were used in the main indirect treatment comparison. These trials were very diverse in both the populations included and in their results. The ERG concludes that, as a result, this analysis did not present reliable evidence on the relative efficacy of vortioxetine compared to other antidepressants.

In terms of cost-effectiveness, the ERG expressed several concerns about the structure of the manufacturer's decision model; in particular the fact that the manufacturer has not attempted to formally consider response in the model, and the fact that the appropriate positioning of vortioxetine within the current treatment pathways has not been fully explored. The manufacturer has assumed that the most appropriate position of vortioxetone is as a second-line treatment (i.e. 1st switch therapy).

The ERG also expressed several uncertainties about the evidence used in the manufacturer's model, the most important being the restricted evidence on relative effectiveness used, the use of STAR*D [ref] to inform prognosis after failure to achieve remission with the initial switch treatment and the use of separate sources of HRQoL data.

Additional exploratory analyses regarding the key areas of structural uncertainty were not deemed feasible within the timelines available to the ERG. Hence the ERG's exploratory analyses focus primarily on those uncertainties surrounding key effectiveness inputs and the outcomes after failure of therapy, and showed these were crucial to cost effectiveness results.

8.3.3 Areas of uncertainty

The relative efficacy of vortioxetine when compared to other antidepressants remains uncertain because of the different sources of evidence considered: trials in the switch population, placebo controlled trials not in the switch population, and trials with active reference arms. All these sources of evidence have problems. There are limited data in the switch population; placebo-controlled trials may not represent the population most likely to receive vortioxetine (i.e. a switch population); active reference arms may be biased in favour of the active reference. Give the different nature of these sources of evidence, and some conflicting results between them, the clinical efficacy of vortioxetine relative to active comparators remains unclear.