**Pharmacoeconomics Review Article**

**Title page**

**The clinical and cost-effectiveness of vortioxetine for the treatment of a major depressive episode in patients who have failed prior anti-depressant therapy: A critique of the evidence.**

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**Running title:** Vortioxetine for the second and third line treatment of a major depressive episode

**Key words:** Vortioxetine, major depressive disorder, major depressive episode

Key points for decision makers

* Only limited data were presented to support the efficacy of vortioxetine as a second-line treatment for major depressive disorder.
* The ERG concluded that, based on the broader evidence, vortioxetine is likely to be similar in efficacy to other analysed antidepressants (citalopram, sertraline, escitalopram and venlafaxine XR), but may be more efficacious than agomelatine and inferior to duloxetine in the treatment of major depression. The ERG concluded that vortioxetine may be more tolerable than other analysed antidepressants (sertraline, venlafaxine XR and bupropion), although the limited data prevents firm conclusions.
* There was considerable uncertainty surrounding the manufacturer’s cost-effectiveness estimates due to limitations in the evidence and the manufacturers’ model.
* Following the Appraisal Consultation Document (ACD), the manufacturer provided a revised economic model considering the cost-effectiveness of vortioxetine as a third-line treatment. In this context, and assuming equal efficacy vortioxetine was shown to be less costly and more effective, owing to its tolerability and adverse event profile, than the relevant comparators.
* The National Institute for Health and Care Excellence (NICE) Appraisal Committee recommended vortioxetine as an option for treating major depressive episodes in adults whose condition has responded inadequately to two antidepressants within the current episode.

# Abstract

The National Institute for Health and Care Excellence (NICE) invited the manufacturer of vortioxetine (Lundbeck) to submit clinical and cost-effectiveness evidence for vortioxetine for the treatment of major depressive episodes (MDEs), as part of the Institute’s Single Technology Appraisal process. The Centre for Reviews and Dissemination and Centre for Health Economics at the University of York were commissioned to act as the independent Evidence Review Group (ERG). This article provides a description of the company submission, the ERG review and the resulting NICE guidance TA367 issued in November 2015. The ERG critically reviewed the evidence presented in the manufacturer’s submission and identified areas requiring clarification, for which the manufacturer provided additional evidence. Two phase III randomised controlled trials for a second-line population involving vortioxetine were identified, REVIVE and TAK318. These two trials represent only 972 patients of over 7,000 patients included in trials of vortioxetine. In REVIVE, there was a statistically significant difference in depression scores favouring vortioxetine compared with agomelatine (mean MADRS scores difference of 2.16 points, 95% CI 0.81 to 3.51). The ERG concluded that, based on all the evidence, rather than the substantially restricted subset of evidence originally considered by the manufacturer, vortioxetine is likely to be similar in efficacy to other analysed antidepressants (citalopram, sertraline, escitalopram and venlafaxine XR), may be more efficacious than agomelatine and inferior to duloxetine. The ERG concluded that vortioxetine may be more tolerable than other analysed antidepressants (sertraline, venlafaxine XR and bupropion), although the limited data prevents firm conclusions. The base case incremental cost-effectiveness ratio (ICER) of vortioxetine reported by the manufacturer was £378 per QALY compared to venlafaxine. Given considerable concerns about the indirect treatment comparison undertaken by the manufacturer, the use of only a restrictive subset of the available evidence, and concerns regarding comparators and structural model assumptions, the ERG believes that this is not a valid estimate of the cost-effectiveness of vortioxetine. Following corrections made to the model made by the ERG, the estimated cost-effectiveness of vortioxetine was sensitive to the source of evidence used, in addition to whether certain comparators were excluded. NICE thus asked the manufacturer to provide a revised economic model, which incorporated the broader evidence base and considered the cost-effectiveness of vortioxetine as a third-line treatment. Assuming equal efficacy vortioxetine was shown to be less costly and generate a higher QALY gainthan relevant comparators at third-line of treatment, owing to its tolerability and adverse event profile. The National Institute for Health and Care Excellence (NICE) Appraisal Committee recommended vortioxetine as an option for treating MDEs in adults whose condition has responded inadequately to two antidepressants within the current episode.

# 1. Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organization responsible for providing national guidance to the NHS in England and Wales on the use of selected new health technologies. Single technology appraisals (STAs) evaluate a single product, device or other technology that has a single indication, for example, a new pharmaceutical product or licensed indication [1]. The manufacturer (or sponsor of the technology) submits the principal evidence supporting the clinical and cost-effectiveness of the product, and an external independent academic organization (the Evidence Review Group [ERG]) is commissioned to produce a review and critique of the evidence submitted [2]. Clinical specialists, NHS commissioning experts and patient experts also provide evidence for consideration by the NICE Appraisal Committee in formulating their guidance [1]. Once published, NICE technology guidance provides a legal obligation for NHS providers to reimburse technologies that have been approved [1]. This article presents a summary of the ERG report and subsequent development of NICE guidance for the use of vortioxetine for the treatment of a MDE with patients who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment.

Full details of the relevant appraisal documents, including the appraisal scope, manufacturer submission, ERG report, Appraisal Consultation Document (ACD), Final Appraisal Determination (FAD) and responses to these documents, can be found on the NICE website [3].

# 2. The Decision Problem

Vortioxetine (brand name Brintellix®) is an antidepressant with a different mechanism of action to other antidepressants such as SSRIs and SNRIs, and has been claimed to act on a number of transmitter systems. The Committee for Medicinal Products for Human Use of the EMA granted marketing authorisation on 18 December 2013 for the treatment of MDEs in people with major depressive disorder (MDD).

The final scope issued by NICE identified a wide range of relevant comparators including SSRIs, SNRIs, tri-cyclic antidepressants (TCAs), other types of antidepressant and augmentation treatments. However, the manufacturer’s submission considered a more restrictive decision problem, limiting attention to a “switch” population defined as patients 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. The manufacturer justified this restriction by highlighting the potential unmet clinical and economic need for more effective and better-tolerated options for this group of patients.

Accordingly, the manufacturer significantly restricted the number of eligible comparators to those which they considered represented alternatives in the proposed switch population. For moderate-to-severe MDEs, NICE Clinical Guideline 90 [4] recommends that when switching to another antidepressant, clinicians should consider switching initially to a different SSRI or a better tolerated newer-generation antidepressant and subsequently to an antidepressant of a different pharmacological class that may be less well tolerated, for example venlafaxine, an older TCA (e.g. amitriptyline) or a monoamine oxidase inhibitor (MAOI, e.g. phenelzine). The manufacturer stated that the tolerability profile of vortioxetine, supported by the clinical efficacy data available within this population, was consistent with their proposed positioning of vortioxetine as an initial switch treatment within existing clinical pathways. The main comparators for vortioxetine as an initial switch therapy were considered by the manufacturer to be SSRIs and better tolerated, newer-generation antidepressants. The SNRIs (e.g. venlafaxine), TCAs and MAOIs were argued by the manufacturer to be reserved for subsequent switches, due to tolerability issues.

Although the ERG acknowledged the justification provided by the manufacturer for restricting the patient population, this was also considered to represent an important limitation from both a clinical and cost-effectiveness perspective. The ERG considered that the appropriate population and potential position of vortioxetine should have been more formally demonstrated by the manufacturer, based on consideration of the full evidence base for vortioxetine and other comparators, rather than restricting the decision population and evidence base from the outset. 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 focused largely on 2 studies considered relevant to the decision problem; REVIVE and TAK318.

# 3. The Independent Evidence Review Group (ERG) Review

The manufacturer provided a submission to NICE on the use of vortioxetine for the treatment of a MDE with patients who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment.

The ERG critically reviewed the evidence presented in the manufacturer’s submission by assessing: (i) whether the submission conformed to NICE methodological guidelines; (ii) whether the manufacturer’s interpretation and analysis of the evidence were appropriate; and (iii) the presence of other evidence or alternative interpretations of the evidence. In addition, the ERG identified areas requiring clarification, for which the manufacturer provided additional evidence [2].

## 3.1 Clinical Evidence

The company conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of vortioxetine for treating individuals with moderate-to-severe MDD who are experiencing an MDE and who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment. Two phase III randomised controlled trials for a second-line population involving vortioxetine were identified, REVIVE and TAK318.

REVIVE was a 12-week, phase IIIb, non-inferiority RCT (n=501), that assessed the efficacy and safety of vortioxetine versus agomelatine in adult patients with MDD who had failed initial antidepressant therapy. Patients were randomised to either vortioxetine (10–20 mg daily; starting dose 10 mg daily), or agomelatine arm (25–50 mg daily; starting dose 25 mg daily). The primary outcome measure was change in Montgomery–Åsberg Depression Rating Scale (MADRS) score from baseline to week 8.[[1]](#footnote-1) Secondary efficacy outcomes included response (defined as ≥50% decrease from baseline in MADRS total score, or a Clinical Global Impression – Improvement scale (CGI-I) ≤2), and remission (defined as a MADRS total score ≤10, or a Clinical Global Impression – Severity scale CGI-S ≤2).

There was a statistically significant difference in depression scores favouring vortioxetine compared with agomelatine (mean MADRS score difference of 2.16 points, 95% CI 0.81 to 3.51). 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%).

Study TAK318 was a multicentre phase IIIb RCT (n=447) that assessed the efficacy and safety of vortioxetine versus escitalopram in patients with well-treated MDD (CGI-S score ≤3) who were experiencing SSRI-induced sexual dysfunction. The population contained within TAK318 therefore represented a subset of the broader switch population where the reason for changing to a different antidepressant may be due to either tolerability issues (of which treatment-emergent sexual dysfunction is one possible example) or efficacy issues. As the primary outcome and population of this trial differed from those of the manufacturer submission’s decision problem, this trial was not formally included in subsequent analyses.

The submission also included a systematic review of treatments other than vortioxetine in the switch population and an indirect treatment comparison with vortioxetine. Four trials were included in the indirect comparison and the outcomes assessed were remission rate and withdrawal rates due to adverse events.

The base case indirect treatment comparison carried out by the company, schematic below (Figure 1), was conducted in a frequentist framework using the Bucher method [5] applied to risk differences, with results reported inTable 1.



Figure 1 – Schematic of company's indirect treatment comparison, adapted from the manufacturer’s submission, available on the NICE website [3]

Table 1 - Summary of the results of the frequentist network meta-analyses

|  |  |  |
| --- | --- | --- |
| **Treatment** | **Remission rate** | **People stopping treatment because of adverse events (withdrawal)** |
| **Rate (%)** | **Risk difference versus vortioxetine (%)** | **95% CI** | **Rate (%)** | **Risk difference versus vortioxetine (%)** | **95% CI** |
| Vortioxetine | 40.5 | n/a | n/a | 5.9 | n/a | n/a |
| Agomelatine | 29.5 | −11.0 | −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 |
| Abbreviation: CI, confidence interval; n/a, not applicable. |

Vortioxetine had higher remission rates than all other treatments, but results were only statistically significant for agomelatine. The indirect treatment comparisons provided by the manufacturer and in Llorca et al. [9] both reported withdrawal due to adverse events, which can be considered a reasonable proxy for tolerability overall. Vortioxetine 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.

### 3.1.1 Critique of the Clinical Evidence

The ERG commented that REVIVE and TAK318 were appropriately conducted but found that the two comparators considered in the trials were only of limited relevance to clinical practice in the UK (NICE has not issued any guidance for Agomelatine - NICE, 2011, and escitalopram is not commonly used). These two trials represent only 972 patients of over 7,000 patients included in trials of vortioxetine. Only four trials were included in the primary indirect comparison of treatments. The ERG considers that the appropriate population and potential position of vortioxetine should have been based on a broader consideration of the evidence for vortioxetine and other comparators.

The ERG stated that the validity of the company’s indirect treatment comparison was highly questionable given the differences in the baseline patient characteristics and severity of conditions of the populations across the four trials. For instance in Kasper et al. [7] it was unclear whether the population consisted entirely of patients receiving second-line treatment. Across the four trials there was considerable variation in the times of outcome assessment (varying from six–14 weeks), which was considered likely to alter results assuming rates of remission and withdrawal are time-dependent. The ERG concluded that the heterogeneous nature of data included in the network meant that the results of any indirect treatment comparison may not be sufficiently reliable.

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. Given the limited nature of the data in the switch population the ERG stated that data in non-switching and first-line populations should have been considered. The ERG noted that the company presented no evidence to suggest that the relative efficacy between non-SSRIs may vary between subsequent lines of treatment. The ERG stated that this restriction was inappropriate and evidence on non-switch populations was relevant when examining the efficacy and safety of vortioxetine. The ERG sought further evidence from the company on first-line population studies during the clarification stage.

The ERG identified two key meta-analyses: Pae et al. [8] and Llorca et al. [9]. Pae et al. [8] contains a meta-analysis of 7 placebo-controlled trials with active reference treatment arms, whereas Llorca et al. [9] consists of an indirect treatment comparison that includes 57 placebo-controlled trials.

The data from Pae et al. [8], comprising of comparisons of vortioxetine with agomelatine (1 trial), duloxetine (5 trials) and venlafaxine (1 trial), were re-analysed by the ERG. The results for the remission outcome are shown below in Table 2.

Table 2 - Remission results from re-analysis of Pae et al. [8]

|  |  |  |
| --- | --- | --- |
| **Treatment** | **Remission rate: odds ratio versus vortioxetine (>1 favours vortioxetine)** | **95% Confidence Interval** |
| Agomelatine | 1.89 | 1.32 to 2.70 |
| Venlafaxine | 0.92 | 0.58 to 1.46 |
| Duloxetine | 0.70 | 0.49 to 1.00 |

Active reference arms are included in trials of antidepressants to assess whether patients are responding to therapy. An active reference should be a drug of proven superiority over placebo, to check whether the trial has successfully treated patients by confirming a difference between the active reference and placebo. In active reference arms, patients known to be non-responsive to the reference were excluded, possibly biasing results in favour of the active reference. While the ERG acknowledged this it did not consider this potential bias to be substantial enough to exclude these trials. Pae et al. [8] found no evidence of any difference in efficacy between vortioxetine and venlafaxine, while vortioxetine was less effective than duloxetine in reducing depression scores, or achieving response and remission[[2]](#footnote-2).

The Llorca et al. [9] indirect treatment comparison includes 57 placebo controlled trials of the following drugs: vortioxetine, agomelatine, desvenlafaxine, duloxetine, escitalopram, sertraline, venlafaxine, vilazodone. A summary of the remission results from this study for relevant comparators for vortioxetine in the switch population under consideration are provided below in Table 3.

Table 3 - Remission results from Llorca et al. [9]

|  |  |  |
| --- | --- | --- |
| **Treatment** | **Remission rate odds ratio versus vortioxetine (>1 favours vortioxetine)** | **P-value of difference versus vortioxetine** |
| Agomelatine | 1.22 | 0.47 |
| Venlafaxine | 0.69 | 0.44 |
| Escitalopram | 0.99 | 0.98 |
| Duloxetine | 0.89 | 0.53 |

Llorca et al. [9] found no evidence of any difference in efficacy between vortioxetine and its comparators. However, there was evidence to suggest fewer people stop vortioxetine due to adverse events compared to other treatments, including sertraline and venlafaxine. The ERG considered that Llorca et al. [9] may provide the most reliable evidence comparing vortioxetine with other treatments.

Consistent with the findings of the company’s indirect treatment comparison, the ERG concluded that, based on all the evidence, rather than the substantially restricted subset of evidence originally considered by the manufacturer, vortioxetine is likely to be similar in efficacy to other analysed antidepressants, but may be more efficacious than agomelatine and inferior to duloxetine. The ERG concluded that vortioxetine may be more tolerable than other analysed antidepressants, although the limited data prevents firm conclusions.

## 3.2 Cost Effectiveness Evidence

The company did not identify any published studies of the cost-effectiveness of vortioxetine in a second-line population. To evaluate cost-effectiveness, the manufacturer’s submission presented a decision model that evaluated the progression of a single MDE. The model was based on treatment success defined in terms of remission at 8-weeks. It followed up patients for 12 months and considered three stages of disease progression: the acute phase (2 months duration), a maintenance phase (6 months duration), and a recovery phase (4 months duration). The model used a decision-tree to evaluate progression within second-line of treatment, and a separate Markov process to describe further lines of therapy that may subsequently be used. The model schematic is reported in Figure 2.

The company conducted the economic analysis from an NHS and personal social services perspective and chose a time horizon of 12 months, negating the need to discount costs and health effects. A half-cycle correction was applied to the health effects but not the costs in the Markov part of the model (cycle length 2 months).



Figure 2 - Model schematic from the manufacturer’s submission, available on the NICE website [3]

The model was populated using various types of studies to inform the parameters. The probability of remission was taken from the indirect comparison conducted by the company, the results of which are in Table 1. The probability of relapse for the maintenance phase was assumed to be the same for all treatments and was sourced from Limosin et al. [10]. The probability of remission and relapse from subsequent lines of treatment were taken from the data obtained for a blend of treatments in STAR\*D [11]. At all lines of treatment, the company considered that patients who had successfully followed six months of maintenance treatment without relapse had recovered. These patients stopped treatment and the company assumed that they could not experience recurrent depression.

Information on costs and HRQoL was obtained from a variety of sources depending upon the phase in the model under consideration. Drug costs were calculated using a combination of trial data and WHO Defined Daily Dose and list prices from Monthly Index of Medical Specialities. Resource use was taken from the PERFORM study for the acute phase and from the Byford, Barrett, Despiégel, & Wade [12] study for longer-term outcomes, applying unit costs from Curtis (2013) [13] and NHS Reference Costs. HRQoL data for health states (e.g. baseline, remission, relapse) were obtained from the REVIVE trial for the acute phase and from Sapin, Fantino, Nowicki, & Kind [14] for the maintenance phase, while disutilities for adverse events were taken from Sullivan, Valuck, Saseen, & MacFall [15].

The base case results presented by the company showed vortioxetine to have an incremental cost-effectiveness ratio (ICER) of £378 per QALY compared to venlafaxine (see Table 4 - Base case results from the ).

Table 4 - Base case results from the manufacturer’s submission, available on the NICE website [3]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Technology** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER (£/QALY)** |
| Venlafaxine | £964 | 0.675 | n/a | n/a | n/a |
| 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 |

### 3.2.1 Critique of the Cost-Effectiveness Evidence

The ERG had a number of significant concerns regarding the model structure employed by the manufacturer. Firstly, the ERG considered the model structure to be unnecessarily complicated and necessitated including additional crude assumptions concerning the timing of particular events. Secondly, the decision to base treatment success and decisions to switch therapy only on remission data reported at 8-weeks was considered an important limitation by the ERG. The third main structural concern identified by the ERG was the assumption that patients do not face a risk of subsequent relapse (or recurrence) in the recovery period. A final major structural limitation of the approach adopted by the manufacturer was the approach to modelling additional lines of treatment and the position of vortioxetine assumed within current sequential treatment. Although the manufacturer incorporated additional lines of therapy (e.g. 3rd-5th lines), the approaches to modelling these additional lines was relatively crude, such that rather than each line representing potentially distinct treatment options, subsequent therapies were assumed to reflect the costs and effects of a combination of different treatment options. While the ERG acknowledged that a full sequential analysis might be considered to be beyond the remit of an STA, the decision to only evaluate the cost-effectiveness of vortioxetine at a single point in the pathway precluded a more appropriate demonstration that this was also the most efficient position. Consequently, this limited the conclusions that could be drawn from the associated results. Without such a consideration it was impossible to establish whether vortioxetine was more or less efficiently positioned as a first line treatment or as a third, fourth or fifth line of treatment.

The ERG commented that basing the decision model around remission data at eight weeks was both unreflective of clinical practice and likely to introduce bias in the resulting estimates of cost-effectiveness. Those patients whose condition responded to treatment partially but had not remitted were treated in the same way in the model as those who had not responded, i.e. were assumed to switch onto third-line treatment at four weeks. The ERG explained that this ignored the costs of additional treatment for people whose disease responded but did not go into remission. The ERG commented that the company also used the eight‑week remission data in its original economic model to inform changes in treatment and utility at four weeks in the model. As a result, the health benefits of patients that went into remission may have been overestimated because the company's model assigned a utility value based on improved health improvements observed at eight weeks rather than four weeks.

At the clarification stage, the company was asked to provide exploratory scenarios investigating the impact of an extended time horizon, given that NICE recommends 2 years of continued treatment in people considered to be at high risk of relapse, and a relaxation of the assumption that patients in recovery receive no treatment or monitoring whilst also having no probability of relapse. The company responded by providing two analyses. One in which a two year time horizon was assumed and another where treatment and monitoring costs were continued in a patient's recovery phase. The company's response showed that the results of their model were robust to these scenarios, but that each increased the ICER associated with vortioxetine.

The ERG highlighted that there was uncertainty around whether STAR\*D was an appropriate study to inform the absolute probabilities regarding the prognosis of people with depression whose condition had not remitted after second-line treatment. This was for two reasons: STAR\*D included treatments that did not reflect the comparators in the model, and the population of STAR\*D was different from the population of REVIVE. Given the absence of other high-quality data to inform parameters at successive lines of treatment, the ERG considered that it would be preferable if STAR\*D was used to inform relative differences between lines of treatment rather than absolute values.

The ERG presented deterministic ICERs for four exploratory analyses for second-line treatment using the company’s original economic model with minor corrections made to utilities and using STAR\*D to inform a proportionate reduction in probability of remission between lines of treatment. To reflect the ERG’s view that the broader evidence should have been considered alongside REVIVE, a series of effectiveness scenarios were explored by the ERG for each of the exploratory analyses:

1. Scenario 1: Assuming relative effectiveness for remission using placebo controlled trials – based on the meta-analysis reported by Llorca et al. [9]
2. Scenario 2: Assuming relative effectiveness for remission using evidence comparing vortioxetine with active comparators – based on the meta-analysis reported by Pae et al. [8]
3. Scenario 3: Assuming equal efficacy for remission.

Table 5 provides the results for these three effectiveness scenarios for the fourth exploratory analysis undertaken, where rate of relapse was assumed to not vary by line of treatment, and where STAR\*D was used to inform a proportionate reduction in effectiveness at each subsequent switch compared to the average of the remission rates for the comparators at initial switch.

Table 5 - ERG exploratory analysis 4 assuming same relapse rate and using average remission rate of 2nd line as basis for subsequent lines’ effectiveness with proportionate reduction between lines of treatment applied based on STAR\*D [with up-titration]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Costs** | **QALYs** | **Incremental** | **ICER** |
| **Costs** | **QALYs** | **with SSRI** | **without SSRI** |
| **(incremental analyses, in relation to next best)** |
| **ERG scenario 1: Llorca et al. (2014)** [9] |
| Escitalopram | £809 | 0.751 | Ref | Ref | Ref | n/a |
| 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. (2015)** [8] |
| Venlafaxine (XR) | £848 | 0.747 | Ref | Ref | Ref | Ref |
| Vortioxetine | £906 | 0.752 | £58 | 0.004 | £13,068 | £13,068 |
| Duloxetine | £951 | 0.755 | £45 | 0.003 | £14,583 | £14,583 |
| Agomelatine | £1011 | 0.739 | £60 | −0.016 | Dominated | Dominated |
| **ERG scenario 3: Equal effectiveness** |
| Escitalopram | £815 | 0.749 | Ref | Ref | Ref | n/a |
| 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 |

It is evident that the results were highly sensitive to the assumptions made concerning the relative effectiveness of the alternative treatments in achieving remission. However, the magnitude of the differences in costs and QALYs between these treatments appeared small across all scenarios. In particular, vortioxetine looks cost-effective when equal effectiveness is assumed and SSRI comparators are excluded, which results from its better tolerability and less severe adverse event profile. One potential justification for excluding SSRI comparators would be if they have already been found to have inadequate response in the patient. This is more likely to be the case in the third, rather than second, line of treatment.

## 3.3 Conclusions of the ERG Review

The manufacturer’s restriction to trials in a “switch” population meant that very limited evidence was presented in the submission and the ERG considers the indirect treatment comparison, in particular, to be unreliable. Trials in the more general, non-switching, population provide more data, but with the possibility that treatment effects may differ from those patients switching treatments, particularly when comparing vortioxetine to SSRIs. Direct comparisons of vortioxetine to other treatments are limited because they are placebo-controlled trials with active reference arms and so there is potential for bias due to them not being truly randomised. These trials, however, suggested that vortioxetine may be inferior to duloxetine, and this possibility cannot be dismissed entirely even with the potential for bias. Indirect comparisons of treatments suggested that vortioxetine had similar efficacy to other drugs, but with the possibility of having a lower withdrawal rate due to adverse events. 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 most other treatments, and so may have a better overall tolerability profile, however data on adverse events with vortioxetine are too limited to draw any firm conclusions on its safety.

There are key structural issues that contribute to the uncertainty surrounding the bias of the estimated ICER in the manufacturer's base case, which is £378 for vortioxetine relative to venlafaxine. In particular, exclusion of first line antidepressant therapy evidence means that the base case model cannot be reliably used for this comparison and should only inform the estimation of cost-effectiveness of vortioxetine against agomelatine. Having corrected utilities used in the model and employed an alternative set of assumptions regarding efficacy for lines of treatment beyond second-line treatments, the ERG found that vortioxetine was dominated by venlafaxine when Llorca et al. [9] evidence was used, when Pae et al. [8] evidence was used vortioxetine had an ICER of £13,068 per QALY relative to venlafaxine (with duloxetine's ICER relative to vortioxetine being £14,583 per QALY), and with assumption of equal effectiveness across treatments vortioxetine had an ICER of £28,270 per QALY relative to escitalopram (SSRI) and an ICER of £7,992 per QALY relative to venlafaxine (SNRI). The ERG considered that this model was preferable to the company's original base case, but that there was still considerable uncertainty owing to restrictive assumptions around the positioning of vortioxetine in the treatment pathway and the exclusion of response from the decision model.

# 4. The National Institute for Health and Care Excellence (NICE) Appraisal Committee: Consideration of All Available Evidence

The Appraisal Committee reviewed the data available on the clinical and cost-effectiveness of vortioxetine, having considered evidence on the nature of MDD and the value placed on the benefits of vortioxetine by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

## 4.1 Preliminary Guidance

Following the first Appraisal Committee meeting, and recorded in the ACD, the Committee stated that it was minded not to recommend vortioxetine within its marketing authorisation, that is, for treating MDEs in adults. The Committee recommended that NICE requested further clarification and analyses from the company, for consideration at a second Appraisal Committee meeting. There was considerable uncertainty regarding whether approving vortioxetine would be cost-effective or not. In particular, assuming equal effectiveness, the ERG had shown that vortioxetine was likely to be cost-effective if SSRIs were excluded as comparators. This would be more appropriate in a third-line setting after SSRIs had failed in first and second line. The Committee therefore requested further analysis in order to clarify this issue and other model structure and parameterisation issues, specifically, the Committee requested new analyses with a revised model structure, use of clinical data pertaining to the broader patient population, and consideration of the cost-effectiveness of vortioxetine as a third-line treatment.

### 4.1.1 Manufacturer’s Response to the ACD Consultation

The company provided additional evidence in its response to the ACD. The additional evidence considered treatment of the third-line population and drew upon evidence from a broader base than the restriction to switch population studies as had been the case in the original submission. The manufacturer also further revised the model to address specific issues raised. Including: defining treatment success, and decisions to switch treatment, by both remission and response (rather than remission alone); adjusting the timing in the model regarding switching of treatment to that in the trials; included a risk of relapse or recurrence at all stages of depression; using the ERG's suggested corrected utility values from REVIVE; including a 24 month time horizon (with discounting of costs and health effects after 12 months); finally, since SSRIs are not used in the UK for a third-line population, SSRIs were not included as relevant comparators.

The company stated that there was no evidence available for the clinical-effectiveness of vortioxetine in people having third-line treatment. In addition to evidence sources and assumptions considered previously - the original indirect treatment comparison, Pae et al. [8], Llorca et al. [9] and equal efficacy - the company also included an additional trial: SOLUTION.

SOLUTION was an international, double-blind, randomised, active-control trial containing 410 East Asian adults assigned to either vortioxetine (10 mg daily) or venlafaxine (150 mg daily). Patients were recruited with recurrent moderate-to-severe MDD and no exclusions were based on the line of treatment used for their current MDE. They were assessed weekly during the first 2 weeks of treatment and then every 2 weeks until the end of the 8 week treatment period. The primary outcome measure in SOLUTION was change from baseline in MADRS score at week 8. The mean change from baseline in MADRS total scores at week 8 was -19.4 points in the vortioxetine group and -18.2 points in the venlafaxine group. This resulted in a non-statistically significant mean difference of -1.2 points in favour of vortioxetine (95% CI −3.0 to 0.6). At week 8, 43.1% of the people’s MDEs had remitted in the vortioxetine group and and 41.4% in the venlafaxine group. The company considered that the SOLUTION trial was relevant to the decision problem because it directly compared vortioxetine with venlafaxine.

The company presented probabilistic pairwise ICERs, as well as a fully incremental analysis, for several scenarios using its revised economic model. The base case results presented in Table 6 represent a model set in primary care, with a six month duration of maintenance therapy following treatment success.

Table 6 - Revised economic model assuming primary care setting and six month maintenance therapy duration

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Costs (£)** | **QALYs** | **Pairwise ICERs (vortioxetine versus comparator)** | **Incremental ICERs** |
| **Scenario: Equal efficacy** |
| Vortioxetine | 1399 | 1.427 | n/a | Ref |
| Venlafaxine | 1400 | 1.410 | Dominant | Dominated |
| Duloxetine | 1549 | 1.411 | Dominant | Dominated |
| Agomelatine | 1567 | 1.428 | £243,0791 | £243,079 |
| **Scenario: Llorca et al. (2014)** [9] |
| Venlafaxine | 1331 | 1.431 | Dominated | Ref |
| Vortioxetine | 1394 | 1.427 | n/a | Dominated |
| Duloxetine | 1526 | 1.424 | Dominant | Dominated |
| Agomelatine | 1582 | 1.424 | Dominant | Dominated |
| 1 South west ICER (£ saved per QALY lost; vortioxetine less costly and less effective) |

Alternative scenarios considered the effects on cost-effectiveness of the following: secondary care setting, implemented by applying different unit costs to resource use; a longer maintenance period of 22 months; and 30% higher resource use of responders compared to remitters. As before, the most stark differences occur when comparing results between different assumptions about the appropriate source of evidence, rather than through changes in the model's structural assumptions. The importance of the choice of source of evidence can be seen in Table 6 where vortioxetine is cost-effective (dominant) at third-line when equal efficacy is assumed, owing to its tolerability and adverse event profile, but is dominated by venlafaxine when effectiveness estimates are taken from Llorca et al. [9]

### 4.1.2 ERG Critique of the Manufacturer’s Response to the ACD Consultation

The company argued that there may be bias arising from the remission and response rates presented in Llorca et al. [9], since for these outcomes several trials' results were missing. The ERG considered that this did not indicate a potential for bias and that the results for the mean change in MADRS score from Llorca, comprised of analysis of all included trials, were consistent with the results for the rates of response and remission.

The ERG stated that SOLUTION was a well-conducted randomised controlled trial. Although it did not reflect the population in England, the ERG considered that there was no reason to suspect that the relative effectiveness between vortioxetine and venlafaxine would differ substantially between patients in East Asia and England. The results from SOLUTION are seen as supporting previously presented evidence that vortioxetine is similarly effective to other non-SSRIs, but may be better tolerated.

The ERG considered that the company’s revised economic model had used the most appropriate available data; and that the revised model structure, featuring both response and remission, more accurately reflected whether a person should continue or change treatment for their MDD in clinical practice in England.

## 4.2 The Appraisal Committee’s Final Guidance

The responses to the preliminary guidance summarised in the ACD [3], and the response submitted by the manufacturer, as well as the ERG’s critique of this, were considered during a second meeting at which the Committee produced a FAD.

Having reviewed the available data on the clinical and cost-effectiveness of vortioxetine, having considered evidence on the nature of MDD and the value placed on the benefits of vortioxetine by people with the condition, those who represent them, clinical experts, and taking into account the effective use of NHS resources, the Committee considered that vortioxetine should be recommended as an option for treating MDEs in adults whose condition has responded inadequately to two antidepressants within the current episode.

The Committee emphasised that there was no convincing clinical-effectiveness evidence to show that vortioxetine was any more or less effective than other antidepressants. However, the Committee highlighted that, across all of the company’s scenarios using its revised economic model, and when assuming equal efficacy between treatments, vortioxetine appeared to be a cost-effective use of NHS resources compared with all other antidepressants.

The FAD forms the basis of the NICE guidance for the use of vortioxetine in the NHS in England and Wales [3].

## 4.3 Key Methodological Issues

### 4.3.1 Clinical Effectiveness

The key methodological issue with respect to clinical efficacy were: (i) the exclusion of broader evidence to inform evidence for second-line treatment for MDD; (ii) limitations of the indirect treatment comparison. The company failed to provide evidence that the relative efficacy of drugs was different between different lines of treatment, in particular between non-SSRI therapies. The ERG considered that this implied the need to use data from the broader evidence set to estimate relative efficacy for the second-line population and not restrict evidence to those collected on the second-line population specifically. The company's indirect treatment comparison was highly limited because it was sparsely populated, and included heterogeneous populations and follow-up durations.

### 4.3.2 Cost-Effectiveness

From the perspective of cost-effectiveness, the restrictive consideration of vortioxetine at a specific line of treatment within a potential sequence of therapies was also the main issue. Not only does the line of treatment affect the relevance of different sources of evidence, as discussed above, but it also has implications for the care setting and the relevant comparators relative to which the incremental costs and health benefits of vortioxetine can be calculated.

The main areas of uncertainty in the cost-effectiveness evidence were (i) the insufficiency of using remission data at eight weeks to solely inform efficacy where response is also clinically relevant and has implications for estimates of cost-effectiveness; (ii) the use of different sources for utilities which belong to different phases of the decision model; (iii) the use of STAR\*D to inform absolute remission and relapse probabilities for successive lines of treatment after second-line treatment; (iv) employing a time horizon of twelve months when NICE recommends continued treatment for at least two years for patients judged to be at high risk of relapse; (v) the assumption of zero probability of relapse following six months of successful maintenance treatment.

# 5. NICE Guidance

Following the consultation on preliminary guidance, the NICE Appraisal Committee released the following final guidance to the NHS (ID583) [3]:

"Vortioxetine is recommended as an option for treating major depressive episodes in adults whose condition has responded inadequately to two antidepressants within the current episode."

# 6. Interpretation of the Guidance

The ERG found that there was no convincing clinical-effectiveness evidence to show that vortioxetine was any more or less effective than other antidepressants, but that it may be more tolerable. Estimates of the cost-effectiveness of vortioxetine, when assuming equal efficacy between treatments, suggested it is an effective use of NHS resources as a third-line treatment compared with all other antidepressants. However, there is a considerable amount of uncertainty owing to a number of assumptions that were made in order to generate the estimates of incremental costs and QALYs, including assumptions around the effectiveness of anti-depressants (including vortioxetine) among the third-line population, given the lack of available evidence.

**Acknowledgements:** This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project number 12/66/01). See the HTA programme website (http://www.hta.ac.uk) for further project information. This summary of the ERG report was compiled after the Appraisal Committee’s review and incorporates additional information and comment from the authors on the STA process and iterations of the NICE guidance not covered by the HTA report. This summary has not been externally peer reviewed by *PharmacoEconomics.*

The ERG would like to thank Paul Blenkiron, Consultant Psychiatrist, Bootham Park Hospital, York, and Catherine Snape, General Practitioner, Jorvik Gillygate Practice, York, who acted as clinical expert advisors to the ERG.

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of NICE or the Department of Health. James Lomas, Alexis Llewellyn, Marta Soares, Mark Simmonds, Kath Wright, Alison Eastwood and Stephen Palmer have no conflicts of interest that are directly relevant to the content of this summary.

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**Author contributions:** James Lomas, Alexis Llewellyn, Marta Soares, Mark Simmonds, Kath Wright, Alison Eastwood and Stephen Palmer all formed part of the ERG that produced the ERG report that this paper describes. James Lomas wrote the first draft of the manuscript. All authors commented on the manuscript and all authors approved the final version.

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1. MADRS is a rating scale measuring severity of depressive episodes consisting of 10 different items, each rated from 0 to 6 [no symptom to severe symptom], contributing to a total score from 0 to 60, where a higher score indicates greater severity. [↑](#footnote-ref-1)
2. The confidence interval does not contain 1 itself with 1.00 being the rounded (up) version of the upper limit, which is 0.996 to three decimal places. [↑](#footnote-ref-2)