National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from the NHS Centre for Reviews & Dissemination and Centre for Health Economics, University of York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by the end of **22 April 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issues 1-7 included within the below proforma are considered major inaccuracies. The remainder are considered moderate-minor and are listed by page number within the ERG report.

Issue 1 Population specified in the decision problem

Description of problem	Description of proposed amendment	Justification for amendment
Lundbeck contests that within the STA process the "optimal position" within a treatment pathway does not have to be demonstrated. It is the manufacturer's prerogative to present data in a subgroup of the population defined in the scope and the products' licence. For example: Page 90: "The ERG considers that the restrictive presentation of the decision problem prevents a full and appropriate consideration of the optimal position of vortioxetine within an existing sequence of treatment options for the management of patients with an MDE".	Removal of statements or explicit recognition at all appropriate points that the manufacturer has the right to identify a subgroup of the population specified within the scope. Statements with a similar sentiment are presented on the following pages and therefore will also require amendment/removal: 10, 20, 28, 32, 39, 58, 95, 123, 125, 126, 142, 144.	Within the STA process a manufacturer is permitted to specify the place in the treatment pathway they wish for a product to be considered regardless of whether this is a subpopulation of the scope or product licence. This point was also raised at the decision problem meeting by the BMJ group (the original ERG for this appraisal). In response to this Elisabeth George reiterated the right/ability of the company to specify their decision problem population. A "demonstration of the most efficient position within the pathway" is therefore not required. In addition, given the high rate of initial treatment failure, the need for efficacious, well tolerated antidepressants in this population is evident. This is recognised within the ERG report and is supported by clinical expert opinion.

Issue 2 Context of the Cochrane Collaboration's comments on the NICE scope: decision problem vs scope

Description of problem	Description of proposed amendment	Justification for amendment
Page 36: In the ERG's discussion of the exclusion of placebo controlled trials they	Removal of statements.	Although the statements cited from the Cochrane Collaboration and NICE were

fail to recognise that the Cochrane Depression Anxiety and Neurosis Group were commenting on potential comparators and the value of placebo controlled trials given the scope. As Lundbeck focussed on a subgroup of patients encompassed by the scope (i.e. switch patients), as justified in the submission, the applicability of the placebo controlled trials of vortioxetine was deemed limited to the decision problem.		made, they have been used out of context and therefore the sentiment of the statements may be misconstrued.

Issue 3 Active reference bias recognised by the EMA rather than the manufacturer

Description of problem	Description of proposed amendment	Justification for amendment
On page 16 the ERG report states that "The manufacturer has criticised the use of active references because…". The current wording of the section reads as if it is only Lundbeck to have recognised the bias associated with active references. In fact the EMA have recognised this in the EPAR for vortioxetine and therefore this should be reflected in the text. A similar statement is made on page 142. This bias should also be recognised when describing the results of Pae 2014 (pg 14).	It should be recognised within the text that within the EPAR for vortioxetine the EMA have stated that comparisons between vortioxetine and active references are invalid. Ensure bias associated with active references is recognised when reporting the results from Pae et al 2014.	Accuracy of reporting to allow an informed interpretation of the results.

In addition, on Page 74 the ERG states: "The potential that results were biased in favour of duloxetine given the potential for bias discussed above must be considered, however there is no evidence of such a bias in favour of venlafaxine". Lundbeck does not believe this statement can be substantiated. If the ERG accepts the potential of bias being present for the comparison versus duloxetine then it should also accept that the same active reference bias is potentially present for the comparison of vortioxetine versus venlafaxine.		

Issue 4 Incorrect assumption regarding the validity of comparison to active reference

Description of problem	Description of proposed amendment	Justification for amendment
Page 74; ERG states "However, the ERG does not consider this risk of bias to be sufficiently substantial to reject such comparisons altogether, particularly as there is a reasonably large number of such with greater numbers of AR trials."	Remove "particularly as there is a reasonably large number of such trials" from this sentence.	The ERG assumes that the number of studies affects the selection bias given with the inclusion of non-responders to an active reference. This is an incorrect assumption since the bias would be consistent across the studies and not diluted with increasing number of completed trials. The number of AR trials has no bearing *per se* on whether the use of AR trials is valid in principle. Indeed, if their use is invalid, as is recognised by the CHMP, then the impact of bias would

		be more serious.

Issue 5 Indirect treatment comparison analyses: outcomes

Description of problem	Description of proposed amendment	Justification for amendment
On page 11 the report states that remission and withdrawals due to adverse events were the only outcomes for which data were presented by Lundbeck. This is true only for the manufacturer's submission. Within the response to the clarification questions data for response and mean change from baseline were also presented as outcomes from the ITC. This should be reflected in the ERG's report.	Include the response and mean change from baseline analyses presented in analyses 18 b and c of Lundbeck's response to clarification questions. The mean change from baseline results show vortioxetine to be statistically significantly better than all comparators included in the analysis (agomelatine, sertraline, venlafaxine and citalopram) in terms of mean change from baseline. The response rate analysis found vortioxetine to be statistically superior to sertraline, venlafaxine and agomelatine (data on response for citalopram was not reported in the Lenox-Smith publication). Similar statements are also presented on the following pages and will also require amendment: 13, 38, 43, 62.	The entirety of the data provided by the manufacturer needs to be reflected accurately. The results for remission and change from baseline should be presented within the ERG report as they allow a fuller understanding of the relative efficacy of vortioxetine when used in the switch population vs the compounds included in the analysis.

Issue 6 Table 27: comments and conclusions in column "Included in MS"

Description of problem	Description of proposed amendment	Justification for amendment
Page 89, Table 27 summarises whether the ERG believes the NICE reference case	Comparators – add comment on the comparators relevant to the switch population with reference to prescribing and clinical	To fairly reflect the decision problem and analyses presented by the manufacturer.

has been adhered to. Lundbeck would like to make comment on the following aspects:
• Comparator(s): Comments column states that comparators used do not represent the full set of comparators as defined in the scope.
  o Lundbeck contests that given the decision problem population is a subgroup of those defined in the scope the comments column should make reference to the comparators deemed relevant given the decision problem based on those used in the UK and those recommended in NICE CG90 for the treatment of the switch population.
• Synthesis of evidence on outcomes: systematic review
  o Lundbeck does not consider the rationale for reporting this as “partially” included in the MS to be robust. Given the points highlighted in Issue 1 above, Lundbeck does not believe this to be appropriate.
• Sensitivity analysis: probabilistic sensitivity analysis
  o Lundbeck is unclear as to why “partially” has been assigned here. The ERG recognise within its comments that probabilistic sensitivity analyses were presented
	guidelines.
	
	Synthesis of evidence on outcomes – update “partially” to “yes”.
	
	Sensitivity analysis: probabilistic sensitivity analysis - update “partially” to “yes”.	

within the submission.		

Issue 7 Power of REVIVE to detect superiority

Description of problem	Description of proposed amendment	Justification for amendment
Page 15: The ERG states that REVIVE may not have been sufficiently powered to demonstrate that vortioxetine is superior to agomelatine. Therefore any inferences from this trial regarding the superiority of vortioxetine over agomelatine may not be reliable as they may be based on chance. This statement is factually inaccurate.	Remove statement as it is incorrect. The following information should be reflected in the ERG report: The MMRM estimates for the mean change from baseline in MADRS total score at Week 8 were -16.5 and -14.4 points in the vortioxetine group and the agomelatine group, respectively, giving a mean difference of -2.16 points in favour of vortioxetine (95% CI: -3.5 to -0.81; p = 0.002) (Please refer to study report 14178A- page 66-67 (see Panel 22)). Non-inferiority was established, as the upper bound of the 95% CI for the vortioxetine and agomelatine comparison was -0.81 MADRS points, and therefore clearly below the non-inferiority margin of +2 MADRS points versus agomelatine. As the two-sided 95% CI for the difference between the means excluded zero and was in favour of vortioxetine, vortioxetine was even superior to agomelatine[1]. Similar statements are also made on pages 45, 52, 58, 79 and 141 and will also require removal.	It is well recognised for non-inferiority studies that once non-inferiority is established one can move to a superiority test under a closed testing procedure[2]. In addition, an obtained significance can never be disregarded using a 'power' argument since the analyses actually did prove powerful enough to detect the difference. A power argument would typically be used in the absence of an achieved significance. The fact that a non-inferiority study provides statistically significant superiority data does not undermine the data reliability. On the contrary, significant secondary analyses strengthen the reliability of the study and therefore strengthen the evidence of vortioxetine being of superior efficacy compared to agomelatine. 1. EMA 2000 'Points to consider on switching between Superiority and non-inferiority

Issue 8 Comments around agomelatine licence in the UK are misleading

Description of problem	Description of proposed amendment	Justification for amendment
Page, 10: Agomelatine is licensed for the treatment of major depressive episodes in the UK but is not recommended by NICE as no evidence submission was made by the manufacturer. In places the report suggests agomelatine is not licensed in the UK.	Page 15, 1st paragraph – 'agomelatine is not approved for use in the UK', should read 'agomelatine is not recommended for use by NICE.' Page 20, 3rd paragraph - 'One compared vortioxetine to a drug not licenced in the UK,' should read 'One compared vortioxetine to a drug not recommended for use by NICE' Amend all additional statements in report. Similar statements are made on pages 79 and 145 and will also require amendment.	Incorrect reporting of agomelatine's marketing authorisation.

Issue 9 Presentation of short-term adverse event data

Description of problem	Description of proposed amendment	Justification for amendment
Page 12: The ERG states "On clarification the manufacturers also supplied adverse event data from 12 short-term placebo controlled trials of vortioxetine". These data were provided within an appendix to the main submission (Appendix 15) and also in the clarification question response.	Statement needs to reflect that these data were presented both in the manufacturer's submission and in response to clarification questions. A similar statement is made on page 65 and will also requirement amendment.	To accurately report the evidence presented by the manufacturer.

Issue 10 Several errors in reporting the results from Llorca et al (2014)

Description of problem	Description of proposed amendment	Justification for amendment
Page 14: there are several errors in the reporting of evidence in table 3 and the sentence preceding the table.	Change following statement is incorrect: "This analysis found no statistically significant evidence of any difference in efficacy between vortioxetine and other antidepressants (except for agomelatine), but did find evidence that vortioxetine had a lower withdrawal rate due to adverse events than venlafaxine, desvenlafaxine and sertraline." The difference in efficacy with agomelatine is not statistically significant. Vortioxetine had a statistically significantly lower	Inaccurate reporting of figures and incorrect conclusions based on the evidence provided.

	withdrawal rate due to AE than venlafaxine, desvenlafaxine and sertraline. Therefore the sentence should be updated as follows : “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 **statistically significantly (p<0.05)** lower withdrawal rate due to adverse events than venlafaxine, desvenlafaxine and sertraline.” Corrections to Table 3 : - Results vs vortioxetine (**Standard error**) to be changed to: Results vs vortioxetine (**p-value**) - Withdrawal (Odds ratio:<1 favours vortioxetine) to be changed to: Withdrawal **due to AE** (Odds ratio:<1 favours vortioxetine) - Remission rate results for agomelatine: 1.220 (0.470)**. The asterisks should be deleted. This table is also included on page 78, (Table 26). The same corrections should be applied here.	

Issue 11 Clarification of sources for meta-analyses

Description of problem	Description of proposed amendment	Justification for amendment
Page 14: The ERG states “Two systematic reviews and one regulatory submission (to the Pharmaceutical Benefits Advisory Committee of Australia)…”. The PBAC is not a regulatory authority but rather an HTA agency.	Statement needs updating to reflect that the submission to the PBAC was an HTA submission rather than a regulatory/licencing submission. Similar statements are also presented on the following pages: 14 (bottom of the same paragraph), 39, 72 and will also require amendment.	Inaccurate statement.

Issue 12 Safety comparisons vs active comparators

Description of problem	Description of proposed amendment	Justification for amendment
Page 15 states “The submission did not present any safety comparisons of vortioxetine with any active comparators, so the safety of vortioxetine compared to other antidepressants is uncertain”. This is incorrect. Safety analyses versus active comparators agomelatine and escitalopram were presented from the REVIVE and TAK318 studies respectively.	Remove as incorrect. A similar statement is made on page 71 and will also require removal.	The statement made is factually inaccurate. Data versus escitalopram and agomelatine were reported from head-to-head studies in the switch population.

Issue 13 Applicability of population included in TAK318 to UK patients

Description of problem	Description of proposed amendment	Justification for amendment
Page 15: In reference to the population included in TAK 318 the report states "The ERG notes that this is a very narrow and specific population, so the TAK318 trial provides little information on the broader population who might take vortioxetine". Lundbeck agrees that the population included in TAK 318 is a subgroup of the licensed population and also of the population addressed in the decision problem. However, the company would contest whether it should be considered "very narrow". Both the literature and clinical opinion support the incidence of sexual dysfunction is high with many antidepressants and is often cited as one of the most common long-term adverse event triggering treatment switch [1,2,3]. 1. Lenderking. W., Samp J., Hanlon J. et al. Factors associated with poor adherence in patients initiating medication for major depressive disorder: Interim results from a	Amend text to: "The ERG notes that this is subpopulation of the population being addressed in the decision problem." A similar statement is made on page 54 and will also require amending.	Text amended to remove subjective and potentially inaccurate representation of the frequency of sexual dysfunction associated with antidepressant treatment.

prospective, longitudinal study. 16th ISPOR European Congress, 2-6 November 2013, Dublin. Poster PMH48 2013. 2. Lenderking. W., Samp J., Hanlon J. et al. Adherence, switching and discontinuation during the 12 weeks following antidepressant initiation in patients with depressive disorder: Results of a prospective longitudinal study. 16th ISPOR European Congress, 2-6 November 2013, Dublin. Poster PMH49 2013. 3. Hunot VM, Horne R, Leese MN, et al. A cohort study of adherence to antidepressants in primary care: the influence of antidepressant concerns and treatment preferences. Primary care companion to the Journal of clinical psychiatry 2007;9:91.		

Issue 14 Classification of severity of depression

The following statement is included on page 23: "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." The manufacturer does not agree that the DSM criteria are not used to classify depression in the UK.	Suggest deleting the second part of the paragraph so it reads: "The submission recognises that the terms MDD and MDE are based on standard classifications from the Diagnostic and Statistical Manual of Mental Disorders (DSM)".	The statement that the DSM criteria are not used in the UK is incorrect. DSM is a globally accepted, widely used diagnostic tool which is also recognised and used in NICE CG90 which states: "After careful review of the diagnostic criteria and the evidence, the Guideline Development Group decided to adopt DSM-IV criteria for this update rather than ICD-10, which was used in the previous guideline (NICE clinical guideline 23). This is because DSM-IV is used in nearly all the evidence reviewed and it provides definitions for atypical symptoms and seasonal depression. Its definition of severity also makes it less likely that a diagnosis of depression will be based solely on symptom counting. In practical terms, clinicians are not expected to switch to DSM-IV but should be aware that the threshold for mild depression is higher than ICD-10 (five symptoms instead of four) and that degree of functional impairment should be routinely assessed before making a diagnosis. Using DSM-IV enables the guideline to target better the use of specific interventions, such as antidepressants, for more severe degrees of depression". Mild/moderate/severe depression is also a distinction made in the DSM, regardless of if the disease is recurrent or not.

Issue 15 Unbalanced comparison of number of chosen trials compared to number of completed trials

Description of problem	Description of proposed amendment	Justification for amendment
Page 27 states "Although vortioxetine has been studied in 24 completed 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" The 7,000 patients included in vortioxetine studies also includes studies in healthy volunteers. Therefore this statement provides an unbalanced and inaccurate view on the relative sizes of the overall vortioxetine efficacy package compared with the number of patients included within the two switch studies.	Statement should be deleted. Similar statements are made on page 10 and 32 will also require deletion.	The large number of patients included in clinical trials with vortioxetine does not only encompass efficacy studies but includes studies in healthy volunteers providing an unbalanced description of how much efficacy data and patient data are covered in the two switch-studies.

Issue 16 Scope of systematic review to identify adverse event data

Description of problem	Description of proposed amendment	Justification for amendment
Page 41 states "The study selection process and eligibility criteria appeared generally appropriate. However, the review of adverse events excluded studies that	Remove statement.	The systematic review was limited to trials based on the following text on Page 30 of the Specification for Manufacturer/Sponsor Submission published in June 2012: "If any of the main trials are designed primarily to

evaluated safety but did not report it as a primary outcome. Therefore there is a risk that relevant studies reporting adverse events may have been missed; as the manufacturer did not provide a record for the exclusion of studies, this risk is difficult to assess." Lundbeck believes that the search undertaken is in line with the instruction provided in the template for manufacturer's submission published in June 2012 for the identification of adverse event data. In addition, though not identified through the systematic review of adverse events, within Appendix 15 the pooled safety data from the short-term studies of vortioxetine identified in through the systematic review of RCTs were included.		assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results". From this statement Lundbeck believes that the instruction given in the template can be interpreted as requesting only adverse event data from trials reporting these as a primary endpoint. In addition, Lundbeck reported the remaining adverse event data in Appendix 15 of the Manufacturer's submission.

Issue 17 Error in Figure 6

Description of problem	Description of proposed amendment	Justification for amendment
Page 51: The key in Figure 6 is incorrect. Instead of reading "PBO" it should read "AGO" as this reports results from REVIVE. Please note, this is an error by Lundbeck which was made in the clarification questions response. Lundbeck have now provided an updated figure to the NICE team.	Please update figure with the updated version as provided by Lundbeck.	The labelling of the key in Figure 6 states the wrong comparator.

Issue 18 Interpretation of CIs in REVIVE results and error in Table 12

Description of problem	Description of proposed amendment	Justification for amendment
Page 50: The ERG states "The relatively wide confidence intervals reflect the uncertainty in true magnitude of the difference in efficacy between vortioxetine and agomelatine." In addition on page 52, Table 12 there is an error. There is a misprint for the results at week 8 (3.51 should be -3.51).	Remove statement and amend table.	The statement presented is highly subjective and gives no basis for the comparison which underpins the claim of relativity. In addition a MADRS SD=7.6 was observed in the study which is lower than what is typically found in depression studies (SD=9.5). In addition with n>220 per group these confidence intervals in fact narrower than what is typically found.

Issue 19 Threshold for depression severity in the UK

Description of problem	Description of proposed amendment	Justification for amendment
On page 60 it is stated that "there is considerable diversity across trials baseline severity. Of particular concern …STAR-D and GSK 2009 both have comparatively low baseline disease severity, below the standard threshold for moderate depression in UK." Lundbeck does not agree that the baseline severity scores in the STAR D study and GSK (2009) – they are above the threshold for moderate depression.	"Below the standard threshold for moderate depression in the UK" should be deleted. Similar statements are made on pages 15 and 141 and will also require amendment.	The statement is incorrect. Baseline HAM-D17 are 18.9 and 19 for STAR-D and GSK (2009) respectively and do correspond to moderate MDD as provided in reference below for HAM-D17[1]: • no depression (0-7); • mild depression (8-16); • moderate depression (17-23); and • severe depression (≥24). 1. Zimmerman, Mark et al. (2013). Severity classification on the Hamilton depression

		rating scale Journal of Affective Disorders, Volume 150, Issue 2, 384 – 388.

Issue 20 Erroneous conclusion of bias

Description of problem	Description of proposed amendment	Justification for amendment
Page 62, includes the following sentence: "Agomelatine may have lower efficacy and higher tolerability than other comparators (as suggested by Llorca et al.),(22) which may have biased the efficacy results of the indirect comparisons in favour of vortioxetine, and negatively biased the withdrawal results." The conclusion of bias here is erroneous. There is no bias within this analysis. The Bucher method has been applied properly, the strength such an analysis over a naïve comparison is the avoidance of the bias of the results.	Remove the statements of bias.	Correctness of the statement.

Issue 21 Incorrect description of differences between agomelatine and vortioxetine safety data

Description of problem	Description of proposed amendment	Justification for amendment
Page 71 includes the following statement: “It may be less safe than agomelatine, although this conflicts with results from REVIVE”.	Please rephrase to “It may be less well tolerated than agomelatine, although this conflicts with results from REVIVE”.	The indirect comparisons indicate that vortioxetine may have a less favourable tolerability profile than agomelatine based on reported withdrawals due to adverse events, but there are no indications of differences in the compounds’ safety profiles.

Issue 22 Unclear description of study types

Description of problem	Description of proposed amendment	Justification for amendment
Page 79: This review identified 12 short-term placebo controlled trials and five longer-term open label trials of vortioxetine.	Change text to: This review identified 12 short-term placebo controlled trials and five longer-term open label extension trials of vortioxetine.	The 5 trials were long-term extension trials to some of the 12 the short term trials and not 5 additional trials.

Issue 23 Concern of misleading conclusion based on available evidence

Description of problem	Description of proposed amendment	Justification for amendment
Page 81: ERG states "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".	Add statement; "However, the ERG's conclusion that vortioxetine may be inferior to duloxetine is based on trials in which duloxetine was included as an active reference, and hence depends critically on the ERG's belief that such a comparison is not substantially biased. It is acknowledged that the CHMP has accepted that comparisons with active references may be invalid".	ERG's conclusion vs. duloxetine cannot be reached from the evidence. It requires a strong assumption about the validity of comparison to active references. ERG presents no scientific evidence to support its dismissal of the CHMP's and Lundbeck's position on this question.

Issue 24 Incomplete review of sensitivity analysis: differential efficacy

Description of problem	Description of proposed amendment	Justification for amendment
Page 115 and following: No mention is made of the threshold sensitivity analysis performed by Lundbeck on remission rate. This is an error of omission, as the analysis is designed specifically to address the question of uncertainty in differential remission rates arising from the shortcomings of the indirect treatment comparison that informs these model inputs	Include section to appraise section 7.7.10.1 of manufacturer submission: Given that the remission rate at 8 weeks was the most influential driver of cost-effectiveness, a threshold analysis was conducted on this variable, in addition to the DSAs reported above. Remission rates were held constant for the comparators to vortioxetine, while the remission rate for vortioxetine was reduced from the base-case value of 40.5% until the ICER reached thresholds of £20,000 and £30,000 per QALY gained in pairwise comparisons with each comparator. In the base case, vortioxetine and venlafaxine formed the cost-effectiveness frontier; the ICER for vortioxetine vs. venlafaxine was £378 per QALY gained. As **Table B1** shows, if the absolute remission rate for vortioxetine is assumed to drop from 40.50% to 30.53%, i.e. a fall of approximately 10% in absolute terms and 25% in relative terms , the ICER for vortioxetine vs. venlafaxine reaches a threshold of approximately £20,000 per QALY gained. Although this assumed remission rate is slightly less than that of venlafaxine, vortioxetine achieves this ICER as a consequence of its superior profile on AEs and withdrawals due to AEs. The table shows the successively lower remission rates at which a similar ICER would result from comparisons with agomelatine, sertraline and citalopram. Corresponding values for a threshold ICER of £30,000 per QALY gained are shown alongside.	The analysis demonstrates the headroom within which vortioxetine is cost-effective in terms of remission rates, an important analysis when ERG does not accept the validity of the remission rates estimated in the ITC.

Table B1. Threshold analysis of remission rates of vortioxetine

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

Figures in **bold** are base case remission rates.

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

Issue 25 Missing text

Description of problem	Description of proposed amendment	Justification for amendment
Page 107: There is text missing from the paragraph in bold: last sentence below Table 35. "The purpose of this request was to develop a greater understanding of how the values in…".	Complete text	Error

Issue 26 Source for maintenance phase doses

Description of problem	Description of proposed amendment	Justification for amendment
Page 110: the ERG states that "The manufacturer makes this assumption through observed increases in dosage from REVIVE". Though this was the case for the doses of agomelatine and vortioxetine, the respective trials included in the indirect treatment comparison in switch were used to inform the maintenance phase doses for the remaining comparators.	Update text to read "The manufacturer makes this assumption through observed increases in dosage for each comparator from the respective trials included in the indirect treatment comparison".	Factual accuracy.

Issue 27 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment
In table 52 (page 130) the value associated with venlafaxine in the Pae paper is reported incorrectly.	The value that is reported is 45.52%. However, it should be 42.52%. The correct value has been used by the ERG in the additional analyses that were run. Therefore the typo does not have any further impact.	The value reported is different to the value presented in the source paper.