NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Vortioxetine for the treatment of major depressive disorder [ID583]

Dear [redacted],

The Evidence Review Group, the Centre for Reviews & Dissemination and Centre for Health Economics at the University of York, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 6 February 2015 by Lundbeck. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data. Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 11 March 2015. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed. Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Martyn Burke, Technical Lead (martyn.burke@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Nicola Hay
Technical Adviser

On behalf of Dr Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Literature searches

A1. Section D, Appendix Table D13: Please provide a rationale for lines 64 to 79 of the search strategy.

A2. Section D, Appendix Tables D33 and D34: Please provide an explanation for the term “2501” in line 13 of these strategies.

A3. Section D, Appendix Table D14: The typographical error in line 44 will have resulted in some records not been identified. Please check whether correcting the typographical error may have led to relevant records being missed.

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REVIVE trial

A4. Patients were enrolled into the REVIVE trial if they received treatment with citalopram, escitalopram, paroxetine, sertraline, duloxetine or venlafaxine monotherapy. Please clarify why patients who received prior treatment with other serotonin reuptake inhibitors [SRIs], such as fluoxetine, were not included.

A5. Please clarify whether patients were allowed to receive additional support (such as GP care or counselling) during the course of the study.

A6. The REVIVE trial is described as being blinded, yet the dose of agomelatine was fixed at 25 mg per day for the first 2 weeks of treatment, whereas the dose of vortioxetine could be changed at week 1. Please clarify further how blinding was retained given this difference in the dose-modification pattern across treatment arms.

A7. Patients were eligible to be enrolled into the REVIVE trial if they were either an inpatient in a psychiatric hospital or an outpatient at a psychiatric setting at the time of the study entry. Please provide the proportion of patients who were inpatients and the proportion who were outpatients at the time they were recruited to the trial.

A8. The REVIVE trial included patients who had depressive symptoms considered as non or partially responsive to no more than one adequate course of SRI monotherapy, and who were candidates for a switch in the investigator’s opinion and wished to change antidepressant treatment. Please clarify whether there were any specific criteria used to define patients as non-responsive or partially responsive.

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TAK318 trial

A9. Please provide details of the recruitment setting for the TAK318 trial (that is, primary care, secondary care).

A10. Patients in the TAK318 trial received treatment with citalopram, paroxetine or sertraline. Please clarify why patients who received prior treatment with other selective serotonin reuptake inhibitors [SSRIs], such as fluoxetine, were not included.

A11. Figure B14 (page of 98 of the company's submission) presents a plot of changes in MADRS and CGI-I scores in the TAK318 trial. Please provide tabulated data on changes in scores used to produce these figures, with mean differences between arms, standard errors and 95% confidence intervals. Please provide similar data for all depression rating scales measured in the TAK318 trial.

Outcomes

A12. **Priority question**: The final scope issued by NICE lists several outcomes that are not presented in the results section (section 6.5 of the company's submission). Where possible, please provide summary tables and/or figures of results for the following outcomes, or clarify where data were not collected:

a. relapse (including relapse rate and time from remission to relapse)
b. sleep quality (in addition to sleep related adverse events)
c. cognitive dysfunction
d. time to response
e. adverse effects of treatment discontinuation

A13. For each depression rating scale used (for example, Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Depression Rating Scale [HAM-D], Clinical Global Impression - Severity Scale [CGI-S]) please explain what is considered a clinically meaningful change or difference in these scales.

Switching and initial-use trials

A14. **Priority question**: In section 6.1 of the company's submission, it is stated that the relative efficacy of anti-depressants cannot be assumed to be constant between initial and switch usage. Please provide any further supporting evidence for this statement beyond the quoted meta-analysis (Papakostas et al 2008). In particular, please provide any evidence that the relative efficacy of non-selective serotonin reuptake inhibitors (non-SSRIs) will differ between initial and switch usage.

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A15. **Priority question**: Please provide results from meta-analyses or other forms of evidence syntheses based on all randomised controlled trials comparing vortioxetine with an active comparator and/or placebo in initial-use or mixed initial and switching use. Please provide results on the following outcomes, if available:

a. Differences in mean change from baseline in depression rating scales (MADRS, HAM-D, CGI-S etc.) between treatments
b. Relative risks or risk differences in response, remission and withdrawal rates
c. Adverse events (AEs):
    i. Number of discontinuation as a result of AEs
    ii. Number and types of severe adverse events

Indirect treatment comparisons

A16. For the indirect treatment comparison (ITC) analysis, the company assumed that the different definitions of remission across trials (using different depression rating scales) were equivalent and could be pooled in the analysis. Please provide justification for this assumption.

A17. **Priority question**: In the company's submission, the results of its ITC analysis were presented in terms of risk differences. Please present results from the ITC analysis in terms of relative risks.

A18. **Priority question**: Results for the company's ITC are provided for remission and withdrawal rates because of adverse events only.

a. Please state which efficacy and safety outcomes were excluded from the ITC, and why.
b. Please also provide results from similar analyses using response rate as the outcome.
c. Please also provide results from similar analyses using change in depression rating scales from baseline as the outcome (for example, by performing a standardised mean difference analysis). If possible, please provide results for both frequentist and Bayesian models.

A19. Please explain why the TAK318 trial was excluded from the ITC analysis.

A20. Table B39, last line (page 124 of the company's submission): please clarify how the adjusted indirect comparison estimated rate of withdrawals because of AEs was 18.0% for citalopram, compared with 5.3% in the original publication (Lenox-Smith et al. 2008).

A21. Please provide details of the recruitment setting for trials included in the ITC (that is, primary care, secondary care).

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Adverse events

A22. Table B44 (page 133 of the company's submission), please provide the number and percentage of patients with a severe adverse event, and the number of discontinuations because of an adverse event per dosage (2.5-10.0 mg; 15-20 mg).

A23. **Priority question**: The scope of the literature search for adverse event studies was expanded to include 'non-switch populations' (see Section 6.9.1.2 of the company's submission). Given this, please clarify why most vortioxetine trials listed in Table B4, (page 64 of the company's submission), were not included in this review. If available, please provide summary adverse event data, including severe adverse events and discontinuation because of an adverse event, for all trials of vortioxetine and for all comparator treatment arms (including placebo). For example, by providing relative risks or risk differences between treatments, and results from meta-analyses, if these have been performed.

Section B: Clarification on cost-effectiveness data

Model time horizon

B1. It is noted that the recovery period in the company's economic model denotes a period of 4 months where the patient is not at-risk. Please carry out exploratory analyses around the time horizon, and present the cost-effectiveness results for time horizons of 2 and 8 months.

B2. According to NICE's guidance on depression in adults (see NICE Clinical Guideline 90), patients at risk of relapse should be treated with anti-depressants for at least 2 years. Please incorporate an additional scenario in the economic model where this is included and present the revised cost-effectiveness results for vortioxetine compared with each of the comparators.

EQ-5D data

B3. **Priority question**: Using results from the REVIVE trial, please provide average baseline and week 8 EQ-5D scores (and associated standard errors) for 'remitters' and 'non-remitters' separately. Please do this separately for those treated with vortioxetine and for those treated with agomelatine, as well as, a combined analysis. Please present the results according to the observed cases [OC], last observation carried forward [LOCF] and mixed model for repeated measures [MMRM] methods (that is, an expanded version of Table B15, page 91 of the company's submission).

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B4. **Priority question**: Using results from the REVIVE trial, please provide average change in EQ-5D scores from baseline at week 8 (and associated standard errors) for remitters and non-remitters separately. Please do this separately for those treated with vortioxetine and for those treated with agomelatine, as well as, a combined analysis. Please present the results according to the OC, LOCF and MMRM methods.

Costs data

B5. It is noted that there is a 'switch cost' associated with changing therapy in the company's economic model. Please justify why this is additional to GP/specialist care visits, and whether switching would take place in primary or secondary care.

Probabilistic analysis

B6. **Priority question**: Please clarify how distributions have been assigned to the model parameter inputs in tables B59 and B60, pages 168 and 171 of the company's submission. Please present the data that underpins them, for example, standard deviation, standard error, number of observations etc.