NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA/MTA)

Vortioxetine for treating major depressive disorder

Response to consultee and commentator comments on the draft scope

Section	Consultees	Comments	Action
Appropriateness	Cochrane Depression Anxiety and Neurosis Group	This topic is appropriate and very relevant, as vortioxetine has recently obtained marketing authorisation throughout the European Union by a centralised authorization process.	Comment noted.
	Depression Alliance	Yes – depression has a significant impact on large numbers of people, and there have been, and still are, a lack of suitable treatment options to allow people to recover. Better access to psychological therapies, improved treatments and more effective peer support would greatly assist people to recover from depression.	Comment noted.
	Lundbeck	Yes, Lundbeck believes it is appropriate for this topic to be referred to NICE for appraisal.	Comment noted.
Wording	Cochrane Depression Anxiety and Neurosis Group	Yes	
	Depression Alliance	Yes	
Timing Issues	Cochrane Depression Anxiety and Neurosis Group	It is of paramount importance to provide timely guidance on the role of vortioxetine in the treatment of depressive episodes, as this antidepressant has only recently been marketed. Therefore, prescribers have not yet placed in therapy this new antidepressant.	Comment noted.
	Depression Alliance	Improved treatments for depression would have a significant impact in improving lives and reducing cost to the NHS, and so should be a	Comment noted.

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		priority	
Background information	Cochrane Depression Anxiety and Neurosis Group	Good	
	Depression Alliance	The background information does not comment on the uncertainty over the prevalence of depression, and the potential under-diagnosis of the condition. It also does not mention the importance of patient choice when an antidepressant is prescribed.	Comment noted. The background has been updated to reflect the first comment received. The guideline covers the importance of patient choice.
	Lundbeck	Lundbeck believes the following points should be highlighted within the background information section: Major depressive disorder is referred to by many synonymous terms, for example: clinical depression, major depression, unipolar depression, clinical depression, depression. Major depressive disorder is characterised by the occurrence of one or more major depressive episodes. A major depressive episode is not a diagnosis in itself but the clinical manifestation of major depressive disorder which is the diagnosis. Moderate-to-severe depression has a grave impact on patients' functioning and therefore their ability to perform daily activities such as going to work, household chores etc. Switching antidepressants within a single major depressive episode is common, with estimated rates of switching from first-line treatment as high as 39.6%~~1~~ and 43.2%~~2~~. The pathway described by CG90 specifies 4 steps rather than the 3 listed within the scope. Initial treatment with a generic SSRI; then an alternative SSRI or a "newer generation, better tolerated" antidepressant; following this, an antidepressant from a different	Comments noted. The background has been updated to reflect most of the comments. Comment noted. The background section has been updated to reflect the steps listed in NICE Clinical Guidance 90.

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		pharmacological class that may be less well tolerated; and finally combination/augmentation of treatment.	
The technology/ intervention	Cochrane Depression Anxiety and Neurosis Group	Good	Comment noted.
	Lundbeck	Lundbeck believes the following changes to the wording of the mechanism of action would add clarity: Vortioxetine (Brintellix, Lundbeck) is a multimodal antidepressant that is thought to exhibit its clinical effect through a combination of 2 pharmacological modes of action: direct modulation of receptor activity and inhibition of the serotonin transporter. To: Vortioxetine (Brintellix, Lundbeck) is a multimodal antidepressant that is thought to exhibit its clinical effect through direct modulation of receptor activity and inhibition of the serotonin transporter. Vortioxetine received marketing authorisation for the treatment of major depressive episodes in adults.	Comments noted. The technology section of the scope has been updated to reflect these comments.
Population	Cochrane Depression Anxiety and Neurosis Group	Good	Comment noted.
	Lundbeck	The population as detailed in the draft scope is in line within licensed population for vortioxetine. However, Lundbeck intends to specify a decision problem that considers only patients with MDEs at a specific stage of the treatment pathway defined in CG90: those at the second step as defined above.	Comment noted. The remit for this appraisal is to appraise vortioxetine within its marketing authorisation.
Comparators	Cochrane	It's interesting to note that placebo is not mentioned as a	Comment noted. No

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	Depression Anxiety and Neurosis Group	comparator. On the one hand we would support this as a goal, as from a policy and clinical perspective, it is important to establish how vortioxetine compares with all other antidepressants. On the other hand, we would expect that excluding placebo-controlled studies as comparators will lead to the exclusion of most randomized comparisons (one of our authors had a preliminary look and found Vortioxetine might only have been tested against Escitalopram, Venlafaxin, Duloxetin and Agomelatine so far). Although we wouldn't challenge the key comparisons being made here, we do wonder if the scope should be widened to make best use of the available data on Vortioxetine, by considering placebo-controlled trials as part of a network meta-analysis. This will enable NICE to consider all the comparative data to inform decision-making.	treatment (placebo) is not established practice in the UK. Placebo does not need to be included as a comparator in the scope in order for the company to be able to conduct a network meta-analysis including studies that compare the intervention with placebo.
	Lundbeck	The draft scope includes a comprehensive list of comparators covering the entire CG90 pathway. Lundbeck believes not all are relevant for the proposed positioning of vortioxetine as switch following inadequate response to first-line treatment for an MDE, i.e. step 2 of the pathway.	Comment noted. The remit for this appraisal is to appraise vortioxetine within its marketing authorisation.
Outcomes	Cochrane Depression Anxiety and Neurosis Group	I would clearly state that response and remission will be described as dichotomous outcomes. With respect to the cognitive dysfunction outcome, our authors would like to note that the EMA report suggests that the effect claimed by the manufacturer is data driven – cognition seems not be assessed systematically and only in placebo controlled trials.	Comment noted. Response to treatment and remission of symptoms are considered separately in the scope.
	Depression Alliance	Yes	
	Lundbeck	In the main, yes. Mortality data are unavailable for vortioxetine or comparators as RCT duration generally does not exceed 1 year, nor can mortality reliably be modelled from intermediate endpoints. The following outcomes are also important in the treatment of MDD:	Comment noted. Mortality is a standard outcome needed for QALY calculations.

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		Disability Productivity Family functioning Changes in sexual functioning	Productivity and family functioning are not included in the NICE reference case and outside the remit of a NICE technology appraisal. Changes in sexual function and disability are captured within adverse effects of treatment.
Economic analysis	Cochrane Depression Anxiety and Neurosis Group	Very interesting	Comment noted.
	Depression Alliance	See comments in Innovation	
	Lundbeck	Lundbeck believes that a one-year time horizon is sufficient to capture the costs and benefits associated with the treatment of a single major depressive episode. This is in line with the vast majority of published cost-effectiveness analyses in MDD.	Comment noted. A time horizon shorter than a patient's lifetime could be justified if there is no differential mortality effect between treatment options, and the differences in costs and health-related quality of life relate to a relatively short period (for example, in the case of an acute infection which has no long term sequelae).

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		Depression is also the leading cause of disability worldwide. Mental health problems including depression are a leading cause of absenteeism and presenteeism globally. The majority of jobs available today demand cerebral, not manual, skills. Not surprisingly, people who rely most on these cerebral skills at work identify stress, anxiety or depression as the most serious work-related health problem affecting them. It is patients that have jobs requiring cerebral skills whose workplace performance is likely to be negatively affected; due to the impact that depression has on their ability to function on a day-to-day basis, and the disability associated with MDEs, maintaining performance at work could become more of a challenge. For these reasons it becomes evident just why the societal impact of depression is so marked. Lundbeck proposes that the wider productivity costs associated with depression should be admissible evidence within the scope of this STA. Therefore it is proposed that the scope formally specify such an analysis.	Comment noted. Productivity and wider societal benefits are not included in the NICE reference case. See Guide to the Methods of Technology Appraisal Section 5.1.10. The referral received from the DH did not include any consideration of costs other than those included in the reference case.
Equality	Cochrane Depression Anxiety and Neurosis Group	No comments here	
	Depression Alliance	Depression is known to be associated with socio-economic factors, so it is possible that improved treatments for depression would have a positive impact on protected groups.	Comment noted.
	Lundbeck	In terms of equity considerations, conducting trials in depression proves challenging. An analysis of the Food and Drug Administration (FDA) database has shown that even for known effective and marketed antidepressants, up to 50% of trials had failed to show a statistically significant drug effect (Khan et al., 2002). Characteristics	Comment noted. The issues raised do show how any recommendations for vortioxetine could be

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		of depression as a disorder contributes greatly to this due to the high variability in response, the heterogeneous patients being diagnosed with MDD, the difficulties in objectively measuring the severity of depression and the high placebo effect (Santen, 2008). These challenges, amongst others, are faced across the board in mental health. As a consequence of this much of the investment into mental health from the pharmaceutical industry has been diverted into disease areas, particularly physical health where a return on investment is more certain given the regulatory requirements and current national and local cost effectiveness criteria in place in many countries. This has been echoed by the conclusions of a report assessing the rates of research investment by the pharmaceutical industry into mental health: "Despite high prevalence and unmet medical need, major pharmaceutical companies are de-emphasising or exiting psychiatry, thus removing significant capacity from efforts to discover new medicines," Insel, (2012) Despite these difficulties the manufacturer, Lundbeck, is committed to its continued investment into the research and development of innovative medicines in mental health, including depression.	considered unfair in the context of the Equality legislation.
Innovation	Depression Alliance	Consideration of the economic impact may underestimate benefit as depression also has a significant impact on carers and family and friends. Depression also has a large impact on a person's ability to work; returning to work signifies recovery and is a good predictor of this being sustained. This return to work reduces the cost to the state in benefit payments and healthcare and increases the person's contribution through tax and other means (eg charitable giving).	Comment noted.
	Lundbeck	The mode of action of vortioxetine differs from all other classes of antidepressants, including the selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs). The antidepressant effects of SSRIs are attributed to the elevations of serotonin (5-HT), mediated via blockade of the serotonin	Comment noted. The company and other consultees will be able to fully describe why they consider vortioxetine to

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		transporter (SERT). SNRIs mediate their antidepressant effects via elevations of serotonin and also – at higher doses – noradrenaline via blockade of SERT and the norepinephrine transporter (NAT), respectively. Modulation by vortioxetine of 6 pharmacological targets, through 2 modes of action: receptor activity and neurotransmitter reuptake inhibition, and the resulting modulation of neurotransmission in several transmitter systems is assumed to be important for the broad antidepressant activity and favourable tolerability profile of vortioxetine. Its multimodal mechanism may make vortioxetine particularly suitable for patients who do not respond adequately to SSRIs or SNRIs or patients who cannot tolerate these types of antidepressants. Lundbeck is currently undertaking further clinical trials to investigate the effect of vortioxetine in patients with cognitive dysfunction as a result of MDD, including those failing first line (SSRI/SNRI) therapies.	be innovative in their evidence submissions, which will then be considered by the Appraisal Committee.
Questions for consultation	Cochrane Depression Anxiety and Neurosis Group	**Is the term 'major depressive episodes' used in clinical practice in England? If so, how does a diagnosis of major depressive episode differ from a diagnosis of major depressive disorder?** Internationally, including WHO, the term 'major depressive episodes' is used. **Have all relevant comparators for vortioxetine been included in the scope?** **Which treatments are considered to be established clinical practice in the NHS for major depression disorder?** Apart from placebo (see above), another comparison group that has not been included is psychological support, which may be similarly effective as compared with antidepressants, in mid-moderate depression. **Are the subgroups suggested in 'other considerations' appropriate?** The subgroup 'people with sexual dysfunction induced by selective serotonin reuptake inhibitors' would imply a different patient	Comments noted. Comment noted. Psychological support is offered at all steps of the treatment pathway, and would not be displaced. Comment noted. This

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		population as compared with the population currently reported in the PICO.	subgroup has been removed from the scope as sexual dysfunction would be captured within adverse effects of treatment.
	Lundbeck	**Is the term 'major depressive episodes' used in clinical practice in England? If so, how does a diagnosis of major depressive episode differ from a diagnosis of major depressive disorder?** As stated within the background information section, a major depressive episode is not a diagnosis in itself; it is a clinical manifestation of major depressive disorder. A patient who has experienced one or more major depressive episodes can be diagnosed with major depressive disorder. Both terms are used within UK clinical practice. **Have all relevant comparators for vortioxetine been included in the scope?** Please see response for "comparators" above. Lundbeck would like to highlight that the relevance of comparators depends on the positioning of vortioxetine within the treatment pathway. **Which treatments are considered to be established clinical practice in the NHS for major depression disorder?** The manufacturer would like to highlight that, again, established clinical practice will be dependent on the positioning of vortioxetine within the treatment pathway. **Have all the relevant outcomes for vortioxetine been included in the scope? In particular, should sleep quality be included as an outcome?** Lundbeck has highlighted thoughts on appropriate outcomes to inform the decision making process in the "outcomes" section above. Further, to address the question above, Lundbeck believes that it is unnecessary to include sleep quality as a stand-alone outcome as	Comments noted. Sleep quality is affected by the condition and has therefore been maintained as a relevant outcome.

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		sleep-related adverse events will be captured as part of the treatment-related adverse effects already included within the scope. **Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom vortioxetine is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Lundbeck believes that the consideration of patients experiencing sexual dysfunction induced by selective serotonin reuptake inhibitors as a separate subgroup is unnecessary. Although it is recognised by Lundbeck that sexual dysfunction is an important treatment-related adverse effect for patients, the scope captures this, along with all other side-effects, by including treatment emergent adverse effects in the list of outcomes. **Where do you consider vortioxetine will fit into the existing NICE pathway, Depression?** Lundbeck proposes that vortioxetine will be positioned within the "newer-generation, better tolerated" treatments within CG90, i.e. as 2nd line, ("switch") treatment for a major depressive episode, after inadequate response (in terms of either efficacy or tolerability) to an SSRI. This positioning is supported by the favourable tolerability profile of vortioxetine demonstrated in the overall regulatory trial programme along with specific phase IIIb trial evidence for the efficacy and tolerability of vortioxetine as switch treatment after a first-line SSRI/SNRI. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In**	Comment noted. Subgroup analysis of people with sexual dysfunction induced by selective serotonin reuptake inhibitors has been removed from the scope as it will be captured as part of treatment related adverse effects. Comment noted.

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		particular, please tell us if the proposed remit and scope: **• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which vortioxetine is licensed;** **• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** **• could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** Please refer to "Other Considerations" above. **Do you consider vortioxetine to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Please refer to "Innovation" section above. **Do you consider that the use of vortioxetine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Depression negatively affects family functioning: it may lead to poorer and decreased communication, increased conflicts, decreased family interaction and decreased intimacy. It is unlikely that patient self-ratings on EQ-5D or other HRQoL instruments capture the spillover effects on family members. Lundbeck has developed and validated a scale to capture the impact of depression on family functioning (the DFFS – Depression and Family Functioning Scale). This scale has been included within some of the phase IIIb trials for vortioxetine. Though the link is yet to be	Comment noted. See response above.

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		made between outputs of this scale and their the impact on HRQoL, given the direct causality from depression it would seem reasonable to include evidence on vortioxetine improving family functioning as relevant for overall assessment of the product value that would not be captured within the QALY.	
Any additional comments on the remit	Cochrane Depression Anxiety and Neurosis Group	We have alerted NICE that we have a Cochrane review underway, entitled 'Vortioxetine for depression in adults' being undertaken by a very experienced group of authors. The protocol is currently being finalised in response to peer-review comments, and we would expect it to be published in the next month or so. We are happy to share this with you (so that you can see, and comment on the current scope of the Cochrane review). We would be very happy to consider trying to organise our timelines to enable us to contribute data etc to the NICE TA (the authors have cited this TA in our protocol). We will certainly keep NICE informed of our timetable and progress if this would be helpful in creating efficiencies/avoiding duplication.	Comment noted. Any input from the Cochrane Depression An xiety and Neurosis Group to this appraisal and future updates to this appraisal are much appreciated.
Comments on the provisional matrix of consultees and commentators	Depression Alliance	Lundbeck believes MQ (patient group) to be a relevant consultee for this consultation.	This organisation has been added as research group.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Merck Sharp & Dohme Ltd.
Pfizer
Department of Health