NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA367; Vortioxetine for treating major depressive disorder

Original publication date:	25 November 2015
Review date	November 2018
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA367, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

There is no new clinical effectiveness or cost data which would warrant reconsideration of the existing recommendations. The marketing authorisation and price of vortioxetine has not changed. It is therefore proposed that technology appraisal (TA) guidance 367 is transferred to the 'static guidance list'.

3. Summary of new evidence and implications for review

New evidence published since the original guidance includes a number of efficacy and safety studies, systematic reviews and meta-analyses. Evidence assessing vortioxetine in people who had inadequate response to a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) therapy, as per the TA367 recommendation, is still limited. However, overall, the new evidence supports the existing recommendation that vortioxetine is an effective and tolerable treatment option for treating major depressive episodes in adults whose condition has responded inadequately to 2 antidepressants within the current episode.

Has there been any change to the price of the technology(ies) since the guidance was published?
The price is the same now as it was at the time of the original appraisal. The price of a pack (28 tablets) of 5 mg, 10 mg or 20 mg tablets is £27.72.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

The marketing authorisation is unchanged, but Lundbeck have told us that they have a

"[redacted] and expect to submit in [redacted] for [redacted]

[redacted]

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

A number of uncertainties were identified in the original guidance, including the treatment pathway, clinical effectiveness, and safety.

In the first committee meeting it was agreed that vortioxetine would not be used as a first line option, and it was not cost-effective as a second-line treatment. Therefore, although the marketing authorisation is indicated "for the treatment of major depressive episodes in adults", the recommendation is specific to 3rd line and beyond. A recent scoping workshop for Esketamine [ID1414] confirmed that vortioxetine is still considered a relevant treatment option for major depressive disorder 3rd line or later (see additional comments). Therefore, there is limited rationale to reconsider vortioxetine as a 1st or 2nd line treatment option.

In its consideration of the original evidence, the committee was not convinced that vortioxetine was more or less effective than other antidepressants. The committee concluded that the indirect comparison used to estimate relative clinical effectiveness was unreliable. Since the publication of the original guidance, a number of reviews have been published. A review found that vortioxetine lead to numerical improvements in remission rate compared to other anti-depressants in people who had inadequate response to SSRI or SNRI therapy (Brignone et al. 2016). Another review of 3 studies in people switching from SSRI/SNRI therapy found that vortioxetine was effective in people who had an inadequate response to SSRI/SNRI (Thase et al. 2017). In a review of 522 trials including people with MDD, vortioxetine was found to be among the more effective antidepressants of those considered (Cipriani et al. 2018). The new evidence suggests that vortioxetine compared to placebo improves depression, cognitive symptoms and functioning, and quality of life (Boulenger et al. 2014; Chokka et al. 2018; Thase et al. 2017). Overall, there is limited evidence of the effectiveness of vortioxetine compared to other antidepressants in people who did not respond to SSRI or SNRI. However, the evidence that is available suggests there may be some benefit from switching to vortioxetine following SSRI or SNRI, however this doesn't significantly impact on the conclusions in the original appraisal.

At the time the original guidance was issued, the adverse effect profile of vortioxetine compared with commonly used antidepressants in England was uncertain. A review of randomised placebo-controlled trials and extension studies including 5701 people with major depressive disorder concluded that vortioxetine was safe and generally well tolerated (Baldwin et al. 2016). In a review of antidepressants, vortioxetine was among the better tolerated of those considered (Thase et al. 2017). The new evidence suggests that vortioxetine is generally well

tolerated, and better tolerated than some other antidepressants (Baldwin et al. 2016; Brignone et al. 2016; Cipriani et al. 2018; Thase et al. 2017).
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
Further work is underway on the update of CG90 which is proposed for publication in Dec 2019. The draft update of CG90 cross refers to the TA367 recommendation. *See Appendix C for a list of related NICE guidance.*
Additional comments
On September 17 there was a scoping workshop for Esketamine (ID1414), a proposed 3rd line treatment option for major depressive disorder. In this workshop the clinical experts confirmed the treatment pathway for MDD, agreeing that vortioxetine is still considered a relevant 3rd line treatment option.

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from November 2014 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

Implementation was raised as a potential issue during consultation on the ACD. The company noted a report by the Royal College of Psychiatrists which noted "people with intellectual disability find it difficult to navigate through services and to negotiate the care they need." In the FAD it is noted that "Potential equality issues raised during the appraisal could not be addressed through NICE technology appraisal guidance."

GE paper sign off: Helen Knight, 21/11/2018

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of vortioxetine within its licensed indication for the treatment of major depressive disorder.

6. Current guidance

Vortioxetine is recommended as an option for treating major depressive episodes in adults whose condition has responded inadequately to 2 antidepressants within the current episode.

People whose treatment with vortioxetine is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

The price of a pack (28 tablets) of 5 mg, 10 mg or 20 mg tablets is £27.72 (excluding VAT; company's submission).

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to (to a specified date)	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	**Yes**
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Agomelatine for the treatment of major depressive episodes (terminated appraisal) (2011) NICE technology appraisal guidance 231

Computerised cognitive behaviour therapy for depression and anxiety (2006) NICE technology appraisal guidance 97

Common mental health problems: identification and pathways to care (2011) NICE guideline CG123

Depression in adults: recognition and management (2009) NICE guideline CG90

Depression in adults with a chronic physical health problem: recognition and management (2009) NICE guideline CG91

Depression in adults (2011) NICE quality standard 8

In progress

Depression in adults: treatment and management NICE guideline update. Publication date to be confirmed

Depression in adults (update) NICE quality standard. Publication expected January 2020

Esketamine for treatment-resistant depression [ID1414] NICE technology appraisal guidance. Publication date to be confirmed

Appendix C

Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Lurasidone (Sunovion)	Phase 3 clinical trials Sunovion [redacted] (June 2018)	[redacted]
Cariprazine (Recordati)	Phase 2 clinical trials UK launch expected [redacted]	[redacted]
Rapastinel (Allergan)	Phase 3 clinical trials UK launch expected [redacted]	[redacted]
Samidorphan and buprenorphine (Akermes)	Phase 2 clinical trials UK launch [redacted]	[redacted]

2. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Vortioxetine has a marketing authorisation in the UK 'for the treatment of major depressive episodes in adults'.	No change - indicated for the treatment of major depressive episodes in adults Source: current SPC (July 2018)
The price of a pack (28 tablets) of 5 mg, 10 mg or 20 mg tablets is £27.72 (excluding VAT; company's submission).	No change - £27.72 per pack of 28 tablets. Source: BNF (2 August 2018)

3. Registered and unpublished trials

Trial name and registration number	Details
An Interventional, Randomised, Double-blind, Parallel-group, Placebo-controlled, Active-referenced (Paroxetine), Fixed-dose Study on the Efficacy of Vortioxetine on Cognitive Dysfunction in Working Patients With Major Depressive Disorder NCT02279966	Purpose: to assess the efficacy of acute treatment with 10 mg/day vortioxetine versus placebo on cognitive performance (focusing on the aspect concerning speed of processing, executive functioning, attention) in working patients Enrollment: 152 Status: completed Start date: October 2014 Completion date: February 2016
An Interventional, Randomised, Double-blind, Parallel-group, Active-comparator, Flexible-dose Study on the Efficacy of Vortioxetine Versus Escitalopram on Cognitive Dysfunction in Patients With Inadequate Response to Current Antidepressant Treatment of Major Depressive Disorder NCT02272517	Purpose: to evaluate the effect of vortioxetine on cognitive dysfunction in major depressive disorder (MDD) patients with inadequate response to current antidepressant treatment. Enrollment: 101 Status: completed Start date: December 2014 Completion date: March 2016

4. Relevant services covered by NHS England specialised commissioning

NHS England (2016) The five year forward view for mental health

NHS England (2017) Mental health in older people: a practice primer

NHS England (2017) Manual for prescribed specialised services 2017/18 Chapter 6 – adult secure mental health services

5. Additional information

Koesters M et al. (2017) Vortioxetine for depression in adults. *Cochrane Database of Systematic Reviews*, Issue 7, CD011520

Appendix D – References

Baldwin DS, Chrones L, Florea I, et al. (2016) The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies. *Journal of psychopharmacology (Oxford, England),* 30(3): 242-52.

Boulenger JP, Loft H, Olsen CK (2014) Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *International clinical psychopharmacology,* 29(3): 138-149.

Brignone M, Diamand F, Painchault C, et al. (2016) Efficacy and tolerability of switching therapy to vortioxetine versus other antidepressants in patients with major depressive disorder. *Current medical research and opinion*, 32(2): 351-66.

Chokka P, Bougie J, Rampakakis E, et al. (2018) Assessment in Work Productivity and the Relationship with Cognitive Symptoms (AtWoRC): primary analysis from a Canadian open-label study of vortioxetine in patients with major depressive disorder (MDD). *CNS spectrums*: 1-10.

Cipriani A, Furukawa TA, Salanti G, et al. (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 391(10128): 1357-1366.

Thase ME, Danchenko N, Brignone M, et al. (2017) Comparative evaluation of vortioxetine as a switch therapy in patients with major depressive disorder. *European neuropsychopharmacology*, 27(8): 773-781.