NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Esketamine for treatment-resistant depression ID1414

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of esketamine within its marketing authorisation for the treatment of major depressive disorder.

Background

Depression, also known as major depressive disorder or clinical depression, is a serious mood disorder that can impact all aspects of daily life. Symptoms typically range from feelings of unhappiness and hopelessness, to a lack of motivation and feeling very tearful. Many people with depression also feel tired constantly, sleep poorly, lose their appetite and exhibit symptoms of anxiety. Depression has often a remitting and relapsing course, and symptoms may persist between episodes. People who do not respond to at least two therapies, are regarded as having treatment-resistant depression. Depression is the leading cause of suicide, accounting for two-thirds of all deaths by suicide.[1]

Each year 6% of adults in England will experience an episode of depression, and more than 15% of people will experience an episode of depression over the course of their lifetime. The average length of an episode is between 6 and 8 months. For many people the episode will be mild, but for more than 30%, the depression will be moderate or severe and have a significant impact on their daily lives. The risk of relapse is high with 50%, 70%, and 90% people relapsing after the first, second, and third episodes respectively.[1] In 2016, there were 2,944 admissions for recurrent depressive disorder (ICD F33) which lead to 3,862 finished consultant episodes and 161,729 bed days.[2]

Women are between 1.5 and 2.5 times more likely to be diagnosed with depression than men. However, men have a higher incidence of suicide, and are less likely to seek help than women.[1]

NICE clinical guideline 90 advocates a stepwise approach for the management of major depressive disorder. When an antidepressant is prescribed, it should normally be a generic selective serotonin reuptake inhibitor (SSRI). If the person with depression develops side effects or their condition has an inadequate response, switching to a different SSRI or a better tolerated newer-generation antidepressant may be considered and increasing the frequency of appointments is recommended. Subsequently an antidepressant of a different pharmacological class, such as tricyclic antidepressants (TCA), or mono-amine oxidase inhibitors (MOI), that may be less well tolerated may also be considered. Antidepressants may then be

combined or augmented with other pharmacological treatments. However, using a single antidepressant is usually associated with a lower side-effect burden. When reviewing treatments after an inadequate response, the adherence to and side effects from the initial treatment are considered. Treatments, that have been inadequately delivered or adhered to, can be re-introduced.

NICE technology appraisal 374 recommends vortioxetine as an option for treating major depressive episodes in adults whose condition has responded inadequately to 2 antidepressants within the current episode.

The technology

Esketamine (Ketanest, Janssen) is a non-competitive glutamate N-methyl-D-aspartate (NMDA) receptor antagonist. Esketamine non-competitively blocks the NMDA receptor and may interact with mu-opioid receptors and sigma receptors, but in the mechanism of antidepressant activity it targets the glutamate NMDA receptor. It is administered intra-nasally.

Esketamine does not have a marketing authorisation in the UK for the treatment of major depressive disorder. It has been studied in randomised clinical trials in combination with an oral antidepressant in adults with treatment resistant depression.

Intervention(s)	Esketamine in addition to established clinical management
Population(s)	Adults with treatment resistant depression, whose condition has responded inadequately to 2 antidepressants within the current episode.

Comparators	• Selective serotonin reuptake inhibitors (for example citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) • Tricyclic antidepressants (for example clomipramine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, and amitriptyline) • Tricyclic-related antidepressants (for example mianserin and trazodone) • Serotonin and noradrenaline reuptake inhibitors (for example venlafaxine, duloxetine and levomilnacipran) • Other antidepressant drugs (for example vortioxetine, agomelatine, mirtazapine, reboxetine and non-reversible mono-amine oxidase inhibitors [such as phenelzine]) • Augmentation or combination treatments (for example, with an antipsychotic such as quetiapine)
Outcomes	The outcome measures to be considered include: • response to treatment (including response rate and time to response) • relapse (including relapse rate and time from remission to relapse) • severity of depression • cognitive dysfunction • remission of symptoms • anxiety • sleep quality • hospitalisation • mortality • adverse effects of treatment (including adverse effects of treatment discontinuation) • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If evidence allows the following subgroups will be considered. These include people with moderate or severe major depressive disorder. In addition, the clinical and cost effectiveness of esketamine may be considered in different positions in the treatment pathway. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Vortioxetine for treating major depressive episodes (2015) NICE Technology Appraisal TA367. Review date: November 2018. Computerised cognitive behaviour therapy for depression and anxiety (2006) NICE technology appraisal guidance TA97. Last updated in May 2013. Review date: after publication of results of the OCTET trial. Related Guidelines: Depression in adults: recognition and management (2009) NICE Clinical Guideline CG90. Review date: last updated in April 2018 and currently under review. Depression in adults with a chronic physical health problem: recognition and management (2009) NICE Clinical Guideline CG91. Review date: to be confirmed. Common mental health problems: identification and pathways to care (2011) NICE Clinical Guideline CG91. Review date: January 2019. Related Quality Standards: Depression in adults (2011). Quality Standards QS8.

	Review date: currently under review with an expected publication date in September 2018. Related NICE Pathways: Depression (2011) NICE pathway.
Related National Policy	National Service Frameworks: Mental Health: modern standards and service models NHS England (2017) Mental health in older people: a practice primer NHS England (2016) The five year forward view for mental health NHS England (2014) NHS England investment in mental health 2015/16 Department of Health (2014) Mental health: priorities for change Department of Health (2013) Making mental health services more effective and accessible Welsh Government (2012) Together for Mental Health: A Strategy for Mental Health and Wellbeing in Wales Department of Health (2012) No health without mental health: implementation framework Department of Health (2011) The mental health strategy for England Department of Health (2009) New Horizons: A shared vision for mental health Department of Health (2007) Commissioning a brighter future: improving access to psychological therapies NHS England (2017) Manual for Prescribed Specialised Services 2017/18 • Chapters 6, 98, 116, 124, and 141. Department of Health and Social Care (2016) NHS Outcomes Framework 2016-2017 • Domains 1, 2, 4 and 5.

Questions for consultation

Have all relevant comparators for esketamine been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for treatment-resistant depression?

Would esketamine be used as a monotherapy, or in combination with an oral antidepressant, as a part of combination therapy, for treatment-resistant depression?

Would esketamine be used before other combination or augmentation therapies would be considered?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom esketamine is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider esketamine will fit into the existing NICE pathway, Depression?

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 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 esketamine will be 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.

Do you consider esketamine 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)?

Do you consider that the use of esketamine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?
- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1 Final scope for CG90: Depression in adults: treatment and management (2015). Accessed May 2018.

2 Hospital Admitted Patient Care Activity, 2016-17: Diagnosis (2017) Hospital Episodes Statistics for England. Inpatient statistics 2016-17. Accessed May 2018.