NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Esketamine for treating major depressive disorder in adults at imminent risk for suicide

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of esketamine nasal spray within its marketing authorisation for treating major depressive disorder in adults at imminent risk for suicide.

Background

Major depressive disorder is a broad condition associated with a range of cognitive, behavioural, emotional and physical symptoms. It has also been referred to as clinical depression, major depression, unipolar depression and depression. Disease severity may vary from mild to severe depending on the number of symptoms and the degree of functional impairment. Symptoms include low mood, loss of pleasure in most activities, hopelessness, lack of motivation and feeling upset. Many people also feel tired constantly, sleep poorly, lose their appetite and exhibit anxiety. In severe disease, psychotic symptoms such as hallucination or delusion may be present. Major depressive disorder often has a remitting and relapsing course, and symptoms may persist between episodes. Depression is the leading cause of suicide, accounting for two-thirds of all deaths by suicide.

Suicidal ideation, sometimes referred to as suicidal thoughts, is defined as 'thinking about, considering, or planning suicide',[1] and falls within the wider category of suicidal behaviour.[2] In 2017, there were 4,451 deaths in England where the cause was identified as suicide,[3] and an estimated 6.7% of adults in England have attempted suicide at some point in their life.[4] Around 6,700 adult hospital admissions in England had a main diagnosis of severe depression in 2017/18.[5] However, it is not known how many of these involved suicidal ideation.

For people with severe depression, NICE Clinical Guideline 90 suggests a combination of antidepressant medication and a high-intensity psychological treatment (cognitive behavioural therapy or interpersonal psychotherapy) can be used. When an antidepressant is prescribed, it is typically a selective serotonin reuptake inhibitor. However, these can cause agitation and lack sedative potential. Tricyclic antidepressants (except for lofepramine) are associated with the greatest risk in overdose. Venlafaxine is associated with a higher risk of death from overdose, compared to other equally effective antidepressants recommended for routine use in primary care.

For people with major depressive disorder who are at imminent risk for suicide, high-intensity psychological interventions are recommended. Electroconvulsive therapy may be appropriate for some patients with life-threatening severe depression, followed by augmentation (one antidepressant used with a non-antidepressant drug) with lithium to improve treatment to avoid relapse. Transcranial direct current stimulation is not widely used as it requires special arrangements for clinical governance and evaluation.

The technology

Esketamine nasal spray (Spravato, Janssen) is a non-competitive, subtype non-selective, activity-dependent glutamate N-methyl-D-aspartate (NMDA) receptor antagonist. It blocks the NMDA receptor and may interact with mu-opioid receptors and sigma receptors. It is administered intra-nasally.

Esketamine nasal spray does not currently have a marketing authorisation in the UK for the treatment of major depressive disorder in adults at imminent risk for suicide. It has been studied in clinical trials in combination with antidepressant treatment, compared with placebo plus antidepressant treatment, in adults aged 18 to 64 years of age with major depressive disorder who are assessed to be at imminent risk for suicide.

Intervention	Esketamine nasal spray in addition to antidepressant treatment.
Population	Adults with major depressive disorder who are at imminent risk for suicide.
Comparators	Established clinical management without esketamine nasal spray, which may include: • Selective serotonin reuptake inhibitors • Tricyclic antidepressants • Monoamine oxidase inhibitors • Inpatient treatment (with full range of high-intensity psychological intervention, such as cognitive behavioural therapy or interpersonal psychotherapy) • High-intensity psychological intervention For acute treatment of people with severe depression that is life-threatening and when a rapid response is required, or when other treatments have failed: • Electroconvulsive therapy, which may be followed by treatment with lithium
Outcomes	The outcome measures to be considered include:

	• response to treatment (including response rate and time to response) • severity of depression and suicidal ideation • suicide risk • remission of symptoms • hospitalisation • functioning (including cognitive) and associated disability • 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	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. Last reviewed: November 2018. Guidance on the use of electroconvulsive therapy (2003). NICE Technology Appraisal TA59. Review date: to be confirmed (last updated in October 2009, and last reviewed in April 2014). Terminated appraisals: Agomelatine for the treatment of major depressive episodes (terminated appraisal) (2011). NICE Technology Appraisal TA231.

	Appraisals in development (including suspended appraisals): Esketamine for treatment-resistant depression NICE technology appraisals guidance [ID1414]. Publication expected March 2020. Related Guidelines: Depression in adults: recognition and management (2009). NICE Clinical Guideline CG90. Review date: last updated in April 2018 and currently under review with an update expected to publish in February 2020. 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 CG123. Last reviewed: August 2018. Preventing suicide in community and custodial settings (2018). NICE Guideline NG105. Review date: to be confirmed. Guidelines in development: Depression in adults: treatment and management. NICE guideline. Publication expected February 2020. Related Interventional Procedures: Transcranial direct current stimulation (tDCS) for depression (2015). NICE interventional procedures guidance IPG530. Related Quality Standards: Depression in adults (2011). NICE quality standard QS8. Review date: currently under review with an expected publication date in November 2019. Suicide prevention. NICE quality standard. Publication expected September 2019. Related NICE Pathways: Depression (2018). NICE pathway. Suicide prevention (2018). NICE pathway. Common mental health disorders in primary care (2018). NICE pathway.
Related National Policy	Department of Health and Social Care (1999) National service framework for mental health

	NHS England (2016) The five year forward view for mental health NHS England (2016) Implementing the five year forward view for mental health • Chapter 8 NHS England (2017) NHS Five year forward view for mental health: one year on NHS England (2017) Mental health in older people: a practice primer NHS England (2016) Specialised Perinatal Mental Health Services (In- Patient Mother and Baby Units and Linked Outreach Teams) Reference: C06/S/a Department of Health and Social Care (2014) Mental health: priorities for change Department of Health and Social Care (2012) No health without mental health: implementation framework Department of Health and Social Care (2011) The mental health strategy for England NHS England (2019) Adult Improving Access to Psychological Therapies programme The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019). NHS manual for prescribed specialist services (2018/2019) • Chapters 6, 116, 124, 141 Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 2, 3, and 5. NHS Outcomes Framework 2016-2017 NHS England (2018) NHS England Funding and Resource 2018/19: Supporting 'Next Steps for the NHS Five Year Forward View'

Questions for consultation

Have all relevant comparators for esketamine nasal spray been included in the scope? Which treatments are considered to be established clinical practice in the NHS for major depressive disorder in those at imminent risk for suicide? How should antidepressant treatment be defined?

How would people at imminent risk for suicide usually be identified in NHS practice? Are there assessment methods such as a questionnaire or other diagnostic tools that are commonly used in NHS practice to identify whether a person is at imminent risk for suicide?

In which NHS setting(s) might esketamine nasal spray for major depressive disorder in those at imminent risk for suicide be administered?

Are the outcomes listed appropriate?

Are there any 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 nasal spray will fit into the existing NICE pathways for Depression, Suicide Prevention, and Common mental health disorders in primary care?

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 nasal spray 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 nasal spray 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 nasal spray 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).

References

1 Klonsky ED, May AM, and Saffer BY (2016) Suicide, Suicide Attempts, and Suicidal Ideation. Annual Review of Clinical Psychology 12:307-330.

2 British Psychological Society (2017) Understanding and preventing suicide: a psychological perspective. Accessed May 2019.

3 Office for National Statistics (2018) Dataset: Suicides in England and Wales by local authority (Table 1).

4 McManus S, Bebbington P, Jenkins R, Brugha T (eds.) (2016) Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014. Leeds: NHS Digital.

5 NHS Digital (2018) Hospital Admitted Patient Care Activity, 2017-2018: Diagnosis.