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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Esketamine for treatment-resistant depression

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of esketamine nasal spray within its marketing authorisation for treatment-resistant depression.

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.

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. Although there is no agreed, commonly used system for classifying the severity of depression, a number of standard outcome measures are available to use in clinical practice which have their own thresholds to provide a distinction between mild, moderate and severe. The risk of relapse is high with 50%, 70%, and 90% people relapsing after the first, second, and third episodes respectively. 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.¹

Women are between 1.5 to 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.

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

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increasing the frequency of appointments is recommended. Subsequently, an antidepressant of a different pharmacological class, such as tricyclic antidepressants (TCA), or monoamine oxidase inhibitors (MAOI) may also be considered. Two antidepressants may be used together, or alternatively one antidepressant used with a non-antidepressant drug (sometimes referred to as augmentation therapy). However, using a single antidepressant is usually associated with a lower side-effect burden. NICE technology appraisal 367 recommends vortioxetine as an option for treating major depressive episodes in adults whose condition has responded inadequately to 2 antidepressants within the current episode. NICE clinical guideline 90 suggests that electroconvulsive therapy should be considered for or acute treatment of severe depression that is life-threatening and when a rapid response is required, or when other treatments have failed. Best supportive care is also an option for people who are intolerant to, or refuse, pharmacological interventions or electroconvulsive therapy.

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 non-competitively blocks the NMDA receptor and may interact with mu-opioid receptors and sigma receptors. It is administered intranasally.

Esketamine nasal spray does not have a marketing authorisation in the UK for the management of treatment-resistant depression. It has been studied in clinical trials in combination with a newly-initiated oral antidepressant in adults with treatment-resistant depression who have had non-response to at least 1 oral antidepressant.

Intervention(s)	Esketamine nasal spray in addition to established clinical management
Population(s)	Adults with treatment-resistant depression.
Comparators	<ul style="list-style-type: none">• Selective serotonin reuptake inhibitors• Tricyclic antidepressants• Monoamine oxidase inhibitors• Serotonin and norepinephrine reuptake inhibitors• Vortioxetine• Combination or augmentation treatments (with lithium or an antipsychotic)• Electroconvulsive therapy• Best supportive care

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Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • 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 • functioning and associated disability • mortality • adverse effects of treatment (including adverse effects of treatment discontinuation) • health-related quality of life.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>
Other considerations	<p>If evidence allows the following subgroups will be considered:</p> <ul style="list-style-type: none"> • by severity of the condition in people with treatment-resistant depression. <p>In addition, the clinical and cost effectiveness of esketamine nasal spray may be considered in different positions in the treatment pathway.</p> <p>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.</p>

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Related NICE recommendations and NICE Pathways	<p>Related Technology Appraisals:</p> <p>Vortioxetine for treating major depressive episodes (2015) NICE Technology Appraisal TA367. Review date: November 2018.</p> <p>Guidance on the use of electroconvulsive therapy (2003) NICE Technology Appraisal TA59. Review date: TBC.</p> <p>Related Guidelines:</p> <p>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.</p> <p>Depression in adults with a chronic physical health problem: recognition and management (2009) NICE Clinical Guideline CG91. Review date: to be confirmed.</p> <p>Common mental health problems: identification and pathways to care (2011) NICE Clinical Guideline CG123. Review date: January 2019.</p> <p>Related Quality Standards:</p> <p>Depression in adults (2011). Quality Standards QS8. Review date: currently under review with an expected publication date in September 2018.</p> <p>Related NICE Pathways:</p> <p>Depression (2011) NICE pathway.</p>
Related National Policy	<p>National Service Frameworks:</p> <p>Mental Health: modern standards and service models</p> <p>NHS England (2017) Mental health in older people: a practice primer</p> <p>NHS England (2016) The five year forward view for mental health</p> <p>NHS England (2014) NHS England investment in mental health 2015/16</p> <p>Department of Health (2014) Mental health: priorities for change</p> <p>Department of Health (2013) Making mental health services more effective and accessible</p> <p>Welsh Government (2012) Together for Mental Health: A Strategy for Mental Health and Wellbeing in Wales</p> <p>Department of Health (2012) No health without mental health: implementation framework</p> <p>Department of Health (2011) The mental health strategy</p>

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	<p>for England</p> <p>Department of Health (2009) New Horizons: A shared vision for mental health</p> <p>Department of Health (2007) Commissioning a brighter future: improving access to psychological therapies</p> <p>NHS England (2017) Manual for Prescribed Specialised Services 2018/19</p> <ul style="list-style-type: none">• Chapters 6, 98, 116, 124, and 141. <p>Department of Health and Social Care (2016) NHS Outcomes Framework 2016-2017</p> <p>Domains 1, 2, 4 and 5.</p> <p>The NHS Long Term Plan, 2019. NHS Long Term Plan</p>
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References

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