

**NIHR Innovation Observatory
Evidence Briefing: December 2017****Esketamine for treatment-resistant depression**

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LAY SUMMARY

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. Approximately half of suicide cases are caused by depression.

Those who do not respond to at least two therapies, are regarded as having ‘treatment-resistant depression.’ Currently there are no approved treatments for patients with depression who are at an imminent risk for suicide. Esketamine is currently in development as a spray through the nose (intranasal) for the treatment of treatment-resistant depression in adults. Compared to treatment options that require injections, esketamine is less invasive and is considered easier to use as it is a nasal spray. If licensed, esketamine may be a safe and effective treatment option for this hard to treat population.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Treatment-resistant depression – third line; add-on and substitute

TECHNOLOGY

DESCRIPTION

Esketamine (ketamine; S-ketamine; JNJ-54135419) is a new molecular entity and 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. The glutamatergic system plays an important role in the neuropathology and treatment of depression as glutamate (L-glutamic acid) is the major excitatory neurotransmitter in the central nervous system and exerts its action through ionotropic glutamate receptors and metabotropic glutamate receptors.¹

Esketamine is currently in development in phase III clinical trials for the treatment of treatment-resistant depression.^{2,3,4,5,6} It is administered intra-nasally 2 times per week at a dose of 28 mg, 56 mg or 84 mg for 4 weeks (induction phase), followed by once every other week, or weekly for those who cannot maintain it (stabilisation and maintenance phase).⁷

Esketamine is licensed widely across Europe as an anaesthetic and analgesic in several of its member states, including the UK, as a solution for injection.⁸ Adverse effects are usually dependent on the dose and speed of injection and are spontaneously reversible. Nervous system and psychiatric (CNS) adverse effects are more common if esketamine is given as the only anaesthetic. Common psychiatric adverse events ($\geq 1/100$ and $< 1/10$) include vivid dreams, nightmares and dizziness. Additional adverse events causing blurred vision, temporary tachycardia, vascular resistance, respiratory depression and vomiting also occur.⁹

INNOVATION and/or ADVANTAGES

Whilst many traditional oral anti-depressants are monoaminergic, directly modulating dopamine, epinephrine/norepinephrine, serotonin and/or melatonin neurotransmitter systems in the body or brain, esketamine acts on the NMDA receptor instead. Antagonising this receptor leads to downstream events that increase the release of glutamate, which enables greater connections between synapses in the brain to be made (synaptic dysfunction can occur in depression). Therefore esketamine has a novel mechanism of action.¹⁰

Additionally, esketamine's development as an intranasal spray is less invasive compared to intravenous administration and is potentially considered easier to use and more preferable.¹¹ Also based on ketamine's potent S-enantiomer, lower doses with fewer side effects are expected from the intranasal formulation of esketamine.¹²

Therefore if licensed, esketamine may be a safe and efficacious treatment option for this difficult to treat population with treatment-resistant depression.

DEVELOPER

Janssen-Cilag Ltd

AVAILABILITY, LAUNCH or MARKETING

Esketamine was awarded Fast Track Designation for major depressive disorder by the US FDA in 2013.¹

Esketamine was designated Breakthrough Therapy for treatment-resistant depression by the US FDA in 2015 and major depressive disorder in 2016.¹

PATIENT GROUP

BACKGROUND

Depression, also known as major depressive disorder or clinical depression, is a serious mood disorder that can impact all aspects of daily life.¹³ The condition affects the thoughts, feelings, behaviour, and physical health of an individual, leading to a range of psychological, physical, and social problems.¹¹ Depression is characterised by persistent low mood and sadness and is often accompanied by long-term dysphoria.¹⁴ Many of the symptoms related to depression, such as lack of energy and self-worth, appetite changes, sadness and suicidal ideation have also been associated with inflammation.¹⁵ However, the exact cause of depression is considered multifactorial. Contributing factors that can lead to the development of depression are difficult experiences in childhood, stressful or traumatic life events, co-morbid mental health conditions, physical health problems, genetic inheritance, a result of medication or alcohol and drug abuse, and poor sleep, diet and exercise.¹⁶

The vast majority of those who experience depression are thought to recover within one year, however, a small portion of these may not recover and after five years or more will show no sign of remission.¹⁷ For patients with major depressive disorder, 30% may reach the treatment goal of remission, whilst the other 50% will either not respond at all or will respond without remission (20%).¹⁸ Patients who do not respond adequately to the appropriate therapy, acquire more difficult to treat depression, and subsequent remission becomes more difficult. After at least two lines of treatment, a greater burden is often presented (e.g. depression becomes chronic with psychiatric comorbidities), therefore reinforcing difficulties in remission.¹⁹

Patients who are resistant to at least two adequately administered physical and or psychological therapies are considered challenging and are described by professionals as patients experiencing 'treatment-resistant depression.'²⁰ Consequently, as the severity of treatment-resistant depression increases, medical costs also increase,²¹ alongside societal burden, reduced quality of life and labour force participation.²² Furthermore, failure of antidepressant therapy is associated with several additional morbidities, one of which is suicidal ideation,²² which is identified as the most important risk factor in the development of depression.²³ Suicidal thoughts may be associated with high mortality and currently those with depression and suicidal ideation require more effective treatment options.²³

CLINICAL NEED and BURDEN OF DISEASE

Depression affects approximately 1 in 10 people in the UK at some point in their life,²⁴ and is more prominent in women compared to men.²⁵ In the UK, the prevalence of major depressive disorder is estimated to be between 5% and 10% of people seen in primary care settings and 10% to 14% of medical inpatients, although the condition may be underdiagnosed.²⁶ Prevalence estimates of treatment-resistant depression generally vary from 10% to 30% in patients with major depression.²⁷

Approximately 90% of people who commit suicide have a psychiatric disorder, with at least 60% of cases caused by depression.²⁸ 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.²⁹

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Vortioxetine for treating major depressive episodes (TA367). November 2015.
- NICE technology appraisal. Guidance on the use of electroconvulsive therapy (TA59). October 2009
- NICE clinical guideline in development. Depression in adults: treatment and management. Expected March 2018.
- NICE clinical guideline. Depression in adults: recognition and management (CG90). Updated April 2016.
- NICE quality standard. Depression in adults (QS8). March 2011 (update expected September 2018).
- NICE interventional procedure guidance. Repetitive transcranial magnetic stimulation for depression (IPG542). December 2015.
- NICE interventional procedure guidance. Transcranial direct current stimulation (tDCS) for depression (IPG530). August 2015.
- NICE interventional procedure guidance. Vagus nerve stimulation for treatment-resistant depression (IPG330). December 2009.
- NICE key therapeutic topic. First-choice antidepressant use in adults with depression or generalised anxiety disorder (KTT8). Updated February 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. The Five Year Forward View for Mental Health. A report from the independent Mental Health Taskforce to the NHS in England. February 2016.

OTHER GUIDANCE

- Qaseem A, Barry MJ, Kansagara D. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Annals of internal medicine*. 2016 Mar 1;164(5):350-9.
- Cleare A, Pariente CM, Young AH, Anderson IM, Christmas D, Cowen PJ, Dickens C, Ferrier IN, Geddes J, Gilbody S, Haddad PM. Evidence-based guidelines for treating depressive disorders with

antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology*. 2015 May;29(5):459-525.

CURRENT TREATMENT OPTIONS

For the majority of people with depression, medication and psychotherapy are effective treatment options.³⁰ However, over-reliance on antidepressants is associated with high mortality and morbidity as medication is ineffective in some patients, or is not being used by the correct patient group.³¹ Additionally, comorbid disorders may also reflect inadequate treatment rather than resistance to treatment,²⁰ as seen in those with treatment-resistant depression. Furthermore the response to treatment from psychological therapy and medication can be influenced by various sociodemographic factors regarding patient beliefs surrounding depression and treatment preference.³²

The following recommendations have been made for the treatment of moderate to severe depression:³²

Overview

For the treatment of moderate to severe depression, an antidepressant combined with a high-intensity psychological treatment (primarily cognitive behavioural therapy (CBT) or interpersonal therapy) should be offered which is informed by:

- Duration of the depressive episode and the development of symptoms
- Previous course of depression and response to treatment
- Likelihood of adherence to treatment and possible adverse events
- Personal treatment preference and priorities

Failure to respond to initial treatment with a selective serotonin reuptake inhibitor (SSRI) may require an increase in the dose, or switching to a different SSRI or mirtazapine. Other second-line choices include lofepramine, moclobemide, and reboxetine. Other tricyclic antidepressants and venlafaxine should be considered for more severe forms of depression; irreversible monoamine oxidase inhibitors should only be prescribed by specialists. Failure to respond to a second antidepressant may require the addition of another antidepressant of a different class, or use of an augmenting agent (such as lithium, aripiprazole [unlicensed], olanzapine [unlicensed], quetiapine, or risperidone [unlicensed]), but such adjunctive treatment should be initiated only by doctors with special experience of these combinations. Electroconvulsive therapy may be initiated in severe refractory depression.³³

EFFICACY and SAFETY

Trial	TRANSFORM-1; NCT02417064; esketamine (experimental dose) + oral antidepressant vs esketamine (experimental dose) + oral antidepressant vs placebo + oral antidepressant; phase III
Sponsor	Janssen Research & Development, LLC
Status	Ongoing
Source of Information	Trial registry ²
Location	EU (not incl UK), USA and other countries
Design	Randomised, active-controlled, placebo-controlled, double-blind study
Participants	n=348 (planned); aged 18-64 years; treatment-resistant depression (not responded to at least 2 prior lines of treatment)
Schedule	<p>Randomised to either:</p> <p><u>Arm 1</u> As part of an initial titration, participants will self-administer 56 milligrams (mg) of esketamine intranasally on day 1, and then 84 mg from day 4 onwards, twice per week for 4 weeks as a fixed dose regimen in double-blind induction phase. In addition participants will simultaneously initiate a new, open-label oral antidepressant (i.e, duloxetine, escitalopram, sertraline, or venlafaxine extended release on day 1 that will be continued for the duration of Double-Blind Induction Phase.</p> <p><u>Arm 2</u> Starting from day 1, participants will self-administer 56 mg of esketamine, intranasally, twice per week for 4 weeks as a fixed dose regimen in double-blind induction phase. In addition participants will simultaneously initiate a new, open-label oral antidepressant (i.e, duloxetine, escitalopram, sertraline, or venlafaxine on day 1 that will be continued for the duration of double-blind induction phase.</p> <p><u>Arm 3</u> Participants will self-administer matching placebo, intranasally, twice per week for 4 weeks as a fixed dose regimen in double-blind induction phase. In addition participants will simultaneously initiate a new, open-label oral antidepressant (i.e, duloxetine, escitalopram, sertraline, or venlafaxine on day 1 that will be continued for the duration of double-blind induction phase.</p>
Follow-up	The study will consist of 3 phases: screening/prospective observational phase (4-7 weeks), double-blind induction phase (4-weeks), follow-up phase (24-weeks). Participants who rollover into a long-term maintenance study will not participate in the follow-up phase
Primary Outcomes	Change From baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at end of double-blind induction phase
Secondary Outcomes	<ul style="list-style-type: none"> • Change from baseline in subject-reported depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9) Total Score at end of double-blind induction. • Onset of clinical response that continued through the end of the double-blind induction phase.

	<ul style="list-style-type: none"> • Change from baseline in subject-reported functioning and associated disability as assessed by the Sheehan Disability Scale (SDS) total score at end of double-blind induction phase. • Number of participants with adverse events and serious adverse events from screening up to end of double-blind induction phase. • Change from baseline in Clinical Global Impression - Severity (CGI-S) score at end of double-blind induction phase. • Change from baseline in subject-reported Generalized Anxiety Disorder (GAD-7) total score at end of double-blind induction phase. • Change from baseline in subject-reported health-related quality of life and health status as assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L) at end of double-blind induction phase.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date August 2018

Trial	TRANSFORM-2, NCT02418585; esketamine + oral antidepressant vs placebo + oral antidepressant, phase III
Sponsor	Janssen Research & Development, LLC
Status	Ongoing
Source of Information	Trial registry ³
Location	EU (not incl UK) and USA
Design	Randomised, active-controlled, placebo-controlled, double-blind study
Participants	n=236; aged 18-64 years; treatment-resistant depression (not responded to at least 2 prior lines of treatment)
Schedule	<p>Randomised to:</p> <p><u>Arm 1</u> Participants will self-administer esketamine intranasally twice per week for 4 weeks as a flexible dose regimen in the double-blind induction phase. All participants will start at a dose of 56 mg on day 1. On day 4, the dose may be increased to 84 mg or remain at 56 mg per investigator's discretion. On days 8 and 11 the dose may be increased to 84 mg (from 56 mg), remain same, or be reduced to 56 mg (from 84 mg) per investigator's discretion. On day 15, a dose reduction from 84 mg to 56 mg is permitted, if required for tolerability; no dose increase permitted. After day 15, dose must remain stable (unchanged). In addition participants will simultaneously initiate a new, open-label oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine extended release on day 1 that will be continued for the duration of double-blind induction phase.</p> <p><u>Arm 2</u> Participants will self-administer matching placebo, intranasally, twice per week for 4 weeks as a flexible dose regimen in Double-Blind Induction Phase. In addition participants will simultaneously initiate a new, open-label oral</p>

	antidepressant (ie, duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]) on Day 1 that will be continued for the duration of Double-Blind Induction Phase.
Follow-up	The study will consist of 3 phases: screening/prospective observational phase (4-7 weeks), double-blind induction phase (4-weeks), follow-up phase (24-weeks). Participants who rollover into a long-term maintenance study will not participate in the follow-up Phase
Primary Outcomes	Change From baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at end of double-blind induction phase
Secondary Outcomes	<ul style="list-style-type: none"> • Change from baseline in subject-reported depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9) Total Score at end of double-blind induction. • Onset of clinical response that continued through the end of the double-blind induction phase. • Change from baseline in subject-reported functioning and associated disability as assessed by the Sheehan Disability Scale (SDS) total score at end of double-blind induction phase. • Number of participants with adverse events and serious adverse events from screening up to end of double-blind induction phase. • Change from baseline in Clinical Global Impression - Severity (CGI-S) score at end of double-blind induction phase. • Change from baseline in subject-reported Generalized Anxiety Disorder (GAD-7) total score at end of double-blind induction phase. • Change from baseline in subject-reported health-related quality of life and health status as assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L) at end of double-blind induction phase.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date January 2018

Trial	TRANSFORM-3, NCT02422186; esketamine + oral antidepressant vs placebo + oral antidepressant, phase III
Sponsor	Janssen Research & Development, LLC
Status	Completed but unpublished
Source of Information	Trial registry ⁴
Location	EU (incl UK), USA and other countries
Design	Randomised, active-controlled, double-blind study
Participants	n=139; aged ≥ 65 years; treatment-resistant depression (not responded to at least 2 prior lines of treatment)
Schedule	Randomised to: <u>Arm 1</u> Participants will self-administer esketamine intranasally twice per week for 4 weeks as a flexible dose regimen in the double-blind induction phase. All

	<p>participants will start with first dose (day 1 as 28 milligram [mg]); second dose (day 4) is either 28 or 56 mg. All subsequent doses may be 28, 56 or 84 mg. After the first dose, all dosing decisions are determined by the investigator based on efficacy and tolerability. In addition participants will simultaneously initiate a new, open-label oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine extended release) on day 1 that will be continued for the duration of double-blind induction phase.</p> <p><u>Arm 2</u> Participants will self-administer matching placebo, intranasally, twice per week for 4 weeks as a flexible dose regimen in double-blind induction phase using the same titration as esketamine. In addition participants will simultaneously initiate a new, open-label oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine extended release) on day 1 that will be continued for the duration of double-blind induction phase.</p>
Follow-up	The study consists of 3 phases: screening/prospective observational phase (4 to 7 weeks), double-blind induction phase (4 weeks), follow up phase (2 weeks). Participants who rollover into a long-term open-label safety study will not participate in the follow-up phase.
Primary Outcomes	Change from baseline in Montgomery Asberg Depression Rating Scale (MADRS) total score at end of double-blind induction phase
Secondary Outcomes	<ul style="list-style-type: none"> • Change from baseline in Clinical Global Impression-Severity (CGI-S) score at end of double-blind induction phase. • Change from baseline in subject-reported health-related quality of life and health status as assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L) at end of double-blind induction phase. • Number of participants with adverse events and serious adverse events from screening up to end of follow-up phase. • Percentage of participants with response ($\geq 50\%$ reduction from baseline in MADRS total score) at the end of double-blind induction phase. • Percentage of participants in remission (MADRS ≤ 12) at the end of double-blind induction phase.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Previously reported as August 2017

Trial	SUSTAIN-1, NCT02493868; esketamine + oral antidepressant vs placebo + oral antidepressant; phase III
Sponsor	Janssen Research & Development, LLC
Status	Ongoing
Source of Information	Trial registry ⁵
Location	EU (not incl UK), USA and other countries
Design	Randomised, active-controlled, placebo-controlled, double-blind study

Participants	n=333; aged 18-64 years; treatment-resistant depression (not responded to at least 2 prior lines of treatment) who are in stable remission after an induction and optimization course of intranasal esketamine plus an oral antidepressant
Schedule	<p>Randomised to:</p> <p><u>Arm 1</u> Direct-entry participants will self-administer esketamine intranasally twice per week for 4 weeks as a flexible dose regimen in the open-label induction phase. Participants will initiate a new oral antidepressant on Day 1 of this phase. Direct-entry and transferred-entry participants will self-administer intranasal esketamine (same dose) at weekly treatment sessions for the first 4 weeks of the optimisation phase, then individualized to either once weekly or once every other week based on depressive symptoms. Participants continue same oral antidepressant treatment from induction phase. During the maintenance phase direct-entry and transferred-entry participants assigned to esketamine will self-administer intranasal esketamine (same dose) once weekly or once every other week based on depressive symptoms. Participants continue same oral antidepressant treatment from induction phase.</p> <p><u>Arm 2</u> Transferred-entry participants will self-administer intranasal placebo at weekly treatment sessions for the first 4 weeks of this phase, then individualized to either once weekly or once every other week based on depressive symptoms. Participants continue same oral antidepressant treatment from induction phase. During maintenance phase direct-entry and transferred-entry participants assigned to intranasal placebo will self-administer intranasal placebo once weekly or once every other week based on depressive symptoms. Participants continue same oral antidepressant treatment from induction phase.</p>
Follow-up	The study will consist of 5 phases: screening/prospective observational phase (4-7weeks) for direct-entry participants only, open-label induction phase (4-weeks) for direct-entry participants only, optimization phase (12-weeks; open-label for direct-entry participants and double-blind for transferred-entry participants), maintenance phase (variable duration; double-blind for all participants) and follow-up phase (2-weeks).
Primary Outcomes	Time to relapse in participants with stable remission who were randomized in the maintenance phase between participant randomization into the maintenance phase and the first documentation of a relapse event (up to an anticipated maximum of 104 weeks)
Secondary Outcomes	<ul style="list-style-type: none"> • Time to relapse in participants with stable response (but not in stable remission) who were randomized in the maintenance phase. • Change from baseline in MADRS total score at end of the maintenance phase in participants who were randomized in this phase. • Change from baseline in subject-reported depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9) total score at end of the maintenance phase in participants who were randomized in this phase. • Change from baseline in Clinical Global Impression - Severity (CGI-S) Score at end of maintenance phase in participants who were randomized in this phase.

	<ul style="list-style-type: none"> • Change from baseline in subject-reported Generalized Anxiety Disorder (GAD-7) score at end of maintenance phase in participants who were randomized in this phase. • Change from baseline in subject-reported health-related quality of life and health status as assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L) at end of maintenance phase in participants who were randomized in this phase. • Change from baseline in Sheehan Disability Scale (SDS) total score at end of maintenance phase in participants who were randomized in this phase. • Number of participants with adverse events and serious adverse events.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date April 2018

Trial	SUSTAIN-2, NCT02497287; open label esketamine + oral antidepressant; phase III
Sponsor	Janssen Research & Development, LLC
Status	Complete but unpublished
Source of Information	Trial registry ⁶
Location	EU (incl UK), USA and other countries
Design	Open-label, non-randomised, uncontrolled study
Participants	n=750 (planned); aged ≥ 18 years; treatment-resistant depression (not responded to at least 2 prior lines of treatment)
Schedule	<p><u>Open-label induction phase</u> Participants will self-administer esketamine intranasally twice per week for 4 weeks as a flexible dose regimen (56 mg or 84 mg). Participants greater than or equal to (>=) 65 will start at a dose of 28 mg on day 1. Direct-entry participants will initiate a new, open-label oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine extended release) on day 1; transferred-entry participants will continue the same oral antidepressant from trial TRANSFORM-3.</p> <p><u>Optimization/maintenance phase</u> Participants will self-administer esketamine (56mg or 84mg for those < 65 years; 28 mg, 56 mg or 84 mg for those ≥ 65 years) intranasally once per week for 4 weeks; transferred entry responder subjects from trial TRANSFORM-3 will start at a dose of 28 mg in the first week. All participants will continue their same oral antidepressant during this phase.</p>
Follow-up	Active treatment for 52 weeks, follow up for 4 weeks.
Primary Outcomes	<ul style="list-style-type: none"> • Change from baseline in Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) score from baseline to follow up phase. • Change from baseline in Cogstate computerized cognitive battery domains and Hopkins Verbal Learning Test-Revised (HVLT-R) from baseline to follow up phase.

	<ul style="list-style-type: none"> Incidence of withdrawal symptoms assessed by Physician Withdrawal Checklist (PWC-20) [at week 52 (end of optimization/maintenance phase) or week 54 (week 2 of follow Up phase) or week 56 (week 4 of follow up phase)].
Secondary Outcomes	<ul style="list-style-type: none"> Number of participants with treatment-emergent adverse events. Change from baseline in heart rate. Change from baseline in systolic and diastolic blood pressure. <p>(For exhaustive list please see trial)</p>
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Previously reported as October 2017

ESTIMATED COST and IMPACT

COST

The cost of esketamine as an intra-nasal spray is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|---|--|
| <input type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input checked="" type="checkbox"/> Other: <i>improved patient convenience and wider societal benefits (e.g. earlier return to normal activities, including employment)</i> | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|--|
| <input type="checkbox"/> Increased use of existing services | <input checked="" type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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