

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Esketamine for treating treatment-resistant depression

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using esketamine in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.**

It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using esketamine in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

**The key dates for this appraisal are:**

Closing date for comments: 18 February 2020

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 5.

# 1 Recommendations

- 1.1 Esketamine with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) is not recommended, within its marketing authorisation, for treating treatment-resistant depression that has not responded to at least 2 different antidepressants in the current moderate to severe depressive episode in adults.
- 1.2 This recommendation is not intended to affect treatment with esketamine that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

## Why the committee made these recommendations

Treatment-resistant depression is managed with oral antidepressants, then a second drug if symptoms do not improve. Electroconvulsive therapy can be used if oral treatments do not work. Drug treatment can also be combined with psychological therapy. Esketamine is a drug treatment taken by nasal spray, supervised by a healthcare professional in a clinic.

Clinical trials suggest that esketamine with an oral antidepressant may be more effective at relieving the symptoms of depression than placebo and an oral antidepressant. But how much benefit it provides over other oral antidepressants with adjunctive therapy or electroconvulsive therapy is unclear because these treatments have not been compared directly. Also, the available evidence did not include psychological therapies.

There is uncertainty about the effect of stopping esketamine treatment. It is unclear if any improvements in symptoms will be maintained after a course of treatment and whether this will improve someone's quality of life. The costs of repeated courses of treatment with esketamine are unknown, as are the costs of providing the clinic service for esketamine.

The cost-effectiveness estimates for esketamine are likely to be much higher than what NICE usually considers to be a cost-effective use of NHS resources. So it cannot be recommended.

## 2 Information about esketamine

### ***Marketing authorisation indication***

2.1 Esketamine (Spravato, Janssen) in combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI), is indicated for adults with treatment-resistant major depressive disorder who have not responded to at least 2 different treatments with antidepressants in the current moderate to severe depressive episode.

### ***Dosage in the marketing authorisation***

2.2 Esketamine is administered from a nasal spray device by the patient under the direct supervision of a healthcare professional. For adults under 65, the starting dose is 56 mg on day 1 with subsequent doses at 56 mg or 84 mg twice a week for the first 4 weeks. In weeks 5 to 8 the drug's summary of product characteristics (SPC) recommends maintaining the dose from week 4 at once weekly intervals. From week 9, 56 mg or 84 mg is recommended in the SPC every 2 weeks or once weekly. Dose adjustments should be made based on efficacy and tolerability to the previous dose. After depressive symptoms improve, the SPC recommends continuing treatment for at least 6 months. The SPC dose recommendations also apply to adults who are 65 and over and for people of Japanese family origin, with the exception that the starting dose on day 1 should be 28 mg, and any dose changes should be in 28 mg increments.

### ***Price***

2.3 The device is single use and delivers 28 mg of esketamine in 2 sprays; one 14 mg spray per nostril. Costs per dose are:

- £163 for a 28 mg dose (one 28 mg device)

- £326 for a 56 mg dose (two 28 mg devices)
- £489 for an 84 mg dose (three 28 mg devices).

Based on the company's economic model, an average course of therapy costs £10,554.25. Costs may vary in different settings because of negotiated procurement discounts.

### 3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Janssen, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

After technical engagement, there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, pages 40 to 44). The committee took these into account in its decision making. It discussed the following issues (issues 1 to 8), which were outstanding.

#### ***The condition and current treatment***

##### **Treatment-resistant depression has a negative effect on people, their families and carers**

- 3.1 The patient expert explained that treatment-resistant depression is associated with a significant burden on all aspects of life, with a range of symptoms. The patient expert emphasised that people living with treatment-resistant depression often have feelings of hopelessness, fear and despair. This can affect the person's family and carers. The clinical expert noted that there is also an impact on the lives of the children of people with treatment-resistant depression. The committee concluded that the condition has a negative effect on people, their families and carers.

##### **There is an unmet need for effective treatment options**

- 3.2 The patient expert explained that people with treatment-resistant depression often feel hopeless because treatments are ineffective. The

clinical expert noted that people will try different courses of treatments to alleviate symptoms. The patient expert highlighted that, when multiple courses of treatment fail, the feelings of hopelessness get worse. They added that this was an inherent aspect of the ‘treatment-resistant’ nature of the condition. The committee acknowledged that the effectiveness of current treatments for treatment-resistant depression is limited and that there is an unmet need for new treatment options for this condition.

## ***Treatment pathway***

### **Current clinical practice includes several different types of treatments**

3.3 The company submission defined treatment-resistant depression as ‘people with major depressive disorder who fail to respond to 2 different oral antidepressants’. It included the recommended treatment pathway for this population from the [NICE guideline on depression](#). Based on the guideline, the [esketamine appraisal scope](#) and the company submission, the treatment options for people with treatment-resistant depression include:

- oral treatments such as sertraline, citalopram, fluoxetine, venlafaxine, vortioxetine, mirtazapine, amitriptyline and monoamine oxidase inhibitors
- augmentation therapy with lithium or an antipsychotic treatment, or combined with another antidepressant
- electroconvulsive therapy (ECT).

The [NICE guideline on depression](#) also includes cognitive behavioural therapy (CBT) as a treatment option combined with these therapies. However, the company noted that the treatment pathway in clinical practice differs from that described in the guideline. The clinical experts explained that the treatment pathway for treatment-resistant depression can vary between services across the country. They explained that there is no general agreement on the definition of treatment-resistant depression. The committee recognised that current clinical practice

includes different types of treatments for treatment-resistant depression, and that there are differing clinical opinions on the definition of the condition.

**The company did not provide evidence comparing esketamine with all relevant comparators**

3.4 The company submission included oral antidepressants as comparators, stating that these were the most common oral treatments for the condition. The clinical expert highlighted that other oral antidepressants as included in the [esketamine appraisal scope](#), sometimes combined, are also used in clinical practice. The committee acknowledged that different treatments are used at different points in the pathway (see section 3.3). The committee heard from other clinical experts who noted that ECT should also be a comparator because the processes involved in administering esketamine are similar to those for ECT. The committee noted that oral antidepressants augmented with lithium or antipsychotic medicines were also included as a comparator in the [esketamine appraisal scope](#), and included in the [NICE guideline on depression](#). The committee acknowledged the company did not provide evidence comparing esketamine with all the relevant comparators listed in the scope, such as combination or augmentation treatments and ECT, were not included as comparators in the company's model.

**The effect of psychological therapy in addition to drug treatments is not clear**

3.5 The patient expert explained that psychological therapy can help alleviate cognitive symptoms and with developing coping strategies. The NICE depression guideline expert noted that psychological therapies were not included as comparators or in combination treatments in the company's submission. The clinical expert explained that CBT is used alongside drug treatment to treat depression. However, not all people with depression can effectively engage with CBT because of the severity of their physical and cognitive symptoms. The patient expert suggested that treatment with esketamine may improve symptoms for enough time to allow people to have CBT. However, the clinical expert added that, because of the

dissociative effects of esketamine treatment, someone would not be able to have psychological therapy immediately after having esketamine. This means that they could not have CBT at the same time as esketamine at their clinic visits. The committee concluded that CBT alongside oral antidepressant therapy and adjunctive therapy is a relevant part of the treatment pathway. But it had not seen any evidence on its effect when combined with esketamine or its comparators.

## ***Clinical effectiveness***

### **Evidence for the treatment benefit of esketamine comes from 2 randomised controlled trials**

3.6 The company's clinical effectiveness evidence came from 2 randomised, double-blind, parallel-group, active-controlled, phase 3 trials. The TRANSFORM-2 and SUSTAIN-1 studies compared a flexible dose of esketamine plus oral antidepressant with placebo plus oral antidepressant in adults aged 18 to 64 with treatment-resistant depression. TRANSFORM-2 included a 4-week screening phase followed by a 4-week induction phase and a 24-week post-treatment follow-up phase. SUSTAIN-1 included a 4-week open-label induction phase followed by a 12-week optimisation phase. People could enter into SUSTAIN-1 either directly as new participants or transferred from TRANSFORM-1 or TRANSFORM-2 if they had stable remission or stable response. The Montgomery-Asberg Depression Rating Scale (MADRS) was used to measure severity of depression and provided the primary outcomes of response, remission and relapse rates. TRANSFORM-2 found significantly improved response rates (69.3% compared with 52%) and remission rates (52.5% compared with 31%) for esketamine over placebo. SUSTAIN-1 found significantly lower relapse rates associated with esketamine treatment compared with placebo for stable remitters (26.7% compared with 45.3%) and for stable responders (25.8% compared with 57.6%). The company also provided supporting evidence from esketamine trials with different doses and populations (TRANSFORM-1



and TRANSFORM-3) and from a long-term safety study (SUSTAIN-2). The committee understood that the TRANSFORM-2 and SUSTAIN-1 results showed an improvement in response, remission and relapse rates for esketamine plus oral antidepressant compared with placebo plus oral antidepressant. However, it noted that some of the studies presented as supporting evidence did not show significant improvements in outcomes. The committee acknowledged the company's attempts to blind the treatments but noted that blinding is difficult, given the dissociative symptoms experienced by people after they had esketamine.

### **The evidence for esketamine is limited in its generalisability to the NHS**

3.7 TRANSFORM-2 and SUSTAIN-1 did not enrol anyone seen in the NHS in England. One UK patient was enrolled in the supporting trial, TRANSFORM-3, and 12 UK patients were enrolled in the long-term safety study, SUSTAIN-2. However, these trials were only used as supporting evidence, and the data were not included as part of the company's model. It is also unclear if the UK patients in the supporting trials were seen in the NHS in England. TRANSFORM-2 and SUSTAIN-1 excluded people:

- with moderate to severe alcohol abuse according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria
- with psychiatric comorbidities
- who had not responded to an adequate course of treatment with ECT in the current major depressive episode
- who had suicidal ideation with intent in the previous 6 months or suicidal behaviour in the previous 12 months.

The ERG noted that the populations excluded from TRANSFORM-2 and SUSTAIN-1 could represent a substantial proportion of people with treatment-resistant depression. It considered that excluding these people limits the generalisability of the trials. The guideline expert noted that excluding people with an acute suicide risk reduces the generalisability of the trials, because people with treatment-resistant depression are likely to have an increased risk of suicide. The clinical experts highlighted that, in

the intervention arm of the trial, esketamine and the oral antidepressant were both newly initiated. They advised that changing multiple treatments at the same time does not reflect clinical practice. The clinical experts acknowledged the limitations of the exclusions but explained that the exclusion criteria is standard for trials in this population. The company indicated that the esketamine marketing authorisation would extend to the people with psychiatric comorbidities that had been excluded from the clinical trials. The committee was aware of the comments in the [European public assessment report](#) (EPAR) about the precautions that need to be taken if esketamine is used in these people. The committee concluded that the extent of the exclusion criteria and the lack of participants from England in the trials mean the evidence for esketamine is limited in generalisability to the NHS population with treatment-resistant depression.

**It is not appropriate to adjust the efficacy estimates of the placebo arm in the trials**

3.8 The company considered that the efficacy estimates (response and remission) for the placebo arm of the TRANSFORM-2 trial were high compared with other studies in this population. The company suggested that the high placebo response rate could be because people visited the clinic more than in clinical practice, respond to the novelty of a nasal spray treatment, have a high expectation of receiving esketamine, and/or respond to the active oral antidepressant given alongside placebo. The company considered that all 4 factors would be present in esketamine treatment in clinical practice but only the response to the active oral antidepressant factor would be present for the comparator. In the 4-week trial induction phase, people who had the placebo nasal spray had 8 clinic visits. People who had esketamine also had 8 clinic visits to preserve blinding. However, the company estimated that in clinical practice people taking oral antidepressants only have 2 visits with healthcare professionals over a 4-week period. The company used a post-hoc adjustment of the TRANSFORM-2 data to model the placebo response

rate with a reduced number of clinic visits. The committee disagreed with the company's approach for the following reasons:

- The committee noted that blinding was an issue in the trials (see section 3.6) and considered that, when people on treatment do not have dissociative effects, some people may realise they are not on esketamine. This would reduce the potential effect of treatment expectation and response to the novel mode of administration.
- The ERG advised that the randomised design of the trial accounts for the placebo effect without the need for any adjustment. The committee also recognised that there would be regression to the mean in both trial arms, and that an adjustment made to just the placebo arm could suppress the regression to the mean and bias results in favour of the intervention (esketamine). The committee concluded that the trial design accounts for placebo effect already, and that adjustment was not appropriate because of the risk of bias. The ERG considered that any adjustment likely overestimates the effect of esketamine treatment and create a bias in its favour. The guideline expert considered that, although the efficacy estimates in the placebo arm seemed higher than expected, the company's method to adjust these was not appropriate.
- The company explained that in the trial, the placebo arm had 6 more clinical visits than would be expected in clinical practice. It considered that these extra clinical visits would improve outcomes and should be removed. The clinical expert highlighted that increased clinical contact could increase the effect of treatment. However, the committee questioned whether the additional clinical contact involved in administering esketamine included psychological therapy. The committee noted that in NHS practice oral antidepressant treatment is ideally combined with CBT, and that this planned and structured clinical contact improves outcomes. However, the committee was not presented with evidence of efficacy of treatments in combination with CBT. The committee also recalled that CBT could not be given at the same time as esketamine (see section 3.5), although it recognised that

people could still have CBT within the same depressive episode. The committee concluded that it had not seen evidence that the additional clinical contact involved in the placebo arm improved clinical outcomes.

The committee concluded that the trial design accounts for placebo effect (from any cause) already, and that adjustment was not appropriate because of the risk of bias. It also considered that it had not seen evidence that the additional contact time during the extra clinic visits in the trials confers clinical benefit. Therefore, the committee concluded that it was not appropriate to adjust the efficacy estimates of the placebo arm in the trials.

## ***Safety***

### **Safety must be taken into account when administering and monitoring esketamine**

3.9 The clinical expert explained that there is no evidence on the effects of withdrawal from esketamine treatment. It is also unclear whether people develop a tolerance to esketamine and need increased doses to achieve the same therapeutic effect. The clinical expert also explained that, if esketamine is given to the people with comorbidities who were excluded from the trials, then the potential for misuse and abuse is increased. The patient expert suggested that a registry could monitor how much esketamine one person receives, and prevent people getting esketamine from more than one source. The clinical expert also suggested a registry for the same reasons. The NHS commissioning expert explained that, because esketamine is a schedule 2 drug, it's subject to the full controlled drug requirements relating to prescriptions and storage. The committee acknowledged that safety must be taken into account when administering and monitoring esketamine to prevent abuse and misuse.

## ***Economic model***

### **A longer time horizon for the economic model is preferred**

3.10 The company's submission indicated that treatment-resistant depression is an episodic condition and modelled a 5-year time horizon to reflect this. The ERG noted that differences in the modelled costs and quality-adjusted life years (QALYs) between treatments continued for 20 years, and so preferred a 20-year time horizon. The committee considered arguments for whether treatment-resistant depression is an episodic or chronic condition. The clinical expert explained that it is difficult to determine when an episode of depression begins or ends and characterised the 'waxing and waning' nature of the condition. On balance, the clinical experts considered treatment-resistant depression to be a chronic condition requiring a longer time horizon. The guideline expert agreed that a longer time horizon was required to account for the duration of the condition and the need for any subsequent treatments. The committee concluded that a longer time horizon better captures the natural history of the condition, and that it preferred the 20-year horizon to the 5-year horizon.

### **There are substantial limitations to the structure of the company's model**

3.11 The ERG highlighted that the company's model structure does not allow for any repeat courses of esketamine treatment. But it does allow for major depressive disorder recurrence after a specified period when people have been in stable remission. The ERG also noted that the modelled effectiveness of subsequent treatments appeared to be underestimated. The patient expert suggested that if treatment with esketamine worked for someone then they would consider having the treatment again when symptoms returned. The committee acknowledged that it had not seen any evidence for the repeated use of esketamine, but considered that it was plausible and would like to explore further with scenario analysis. The ERG advised that the effects of the modelling of subsequent or repeat treatment increased with the time horizon of the

model. The committee considered that, given its preferred time horizon (see section 3.10), the company's modelling of recurrence and subsequent or repeat treatment given does not reflect clinical practice. The committee concluded that the company's model was limited because it did not account for the chronic nature of the condition, underestimates the effectiveness of subsequent treatments, and is unable to include repeat treatments. The committee would like to see a new model with a longer time horizon that allows for repeat treatment.

**There is no evidence on the effect of stopping esketamine after 2 years for reasons other than lack of efficacy**

3.12 The company assumed that people would not stop taking oral antidepressants for any reason other than lack of response. But it assumed that people would stop esketamine treatment for other reasons, in line with the criteria in the SPC and additional discontinuation guidance provided by the company. In the company model, rates of discontinuation (for reasons other than lack of response) for esketamine varied by treatment phase. Based on advice from clinicians, the company modelled that 52% of people stopped treatment after 9 months in stable remission, with 16% expected to continue treatment for more than 2 years. Stopping treatment was assumed to stop incurring the cost of esketamine but have no effect on QALYs. The clinical experts suggested that a proportion of responders who were not in stable remission would discontinue. The committee were aware that in SUSTAIN-1 the rate of relapse increased when esketamine was stopped. The ERG highlighted that no evidence was submitted to determine the effect of discontinuation on symptoms or quality of life. The clinical expert explained that the decision to stop treatment would be done after a full discussion of all the circumstances associated with the individual patient. The patient expert noted that people would be concerned and worried about relapse. The committee recognised that people would be fully involved in the decisions around continuing treatment, and that decisions about how long treatment lasts and reasons for stopping it vary based on individual circumstances. Also,

circumstances are very different in people with comorbidities compared with those without. The committee considered that assuming an indefinite improvement in quality of life after stopping esketamine treatment was implausible. It recognised that people may have changes in MADRS score below the threshold for 'relapse' but that still affect quality of life. The clinical experts supported this view and explained that the MADRS is a non-linear scale, meaning that increases in score at the lower end of the scale represent a larger change in symptoms than at higher points of the scale. The ERG and clinical experts also highlighted that there were no data to accurately determine discontinuation rates. Because of this, the ERG preferred to assume no discontinuation for reasons other than lack of efficacy at 2 years. The committee considered that it's likely that people would stop esketamine for other reasons over a 2-year period, but that it's unclear how many. The committee recognised that, in practice, people who were 'responders' or 'stable remitters' and stopped treatment for reasons other than lack of efficacy could have repeat courses of esketamine, but that this was not accommodated in the model (see section 3.11). The committee concluded that, on balance, without data the least biased estimate of cost effectiveness would be to not include discontinuation of esketamine for reasons other than lack of efficacy.

**It is not appropriate to include an effect of esketamine on mortality**

3.13 In its economic model, the company assumed there were 2 different sources for risk of death: all-cause mortality risk (specific to age and gender) and an excess annual mortality for treatment-resistant depression associated with suicide. The company modelled a reduction in treatment-resistant depression (which is associated with excess mortality), indirectly decreasing the risk of excess mortality when treated with esketamine. The committee considered that it was plausible that esketamine could affect mortality. But the committee concluded that, because of issues with generalisability and the exclusion of people with an acute suicide risk (see section 3.7) and the lack of data, it could not accept a reduced suicide

risk, and therefore did not accept a reduced mortality risk with esketamine treatment.

## **Utilities**

### **Applying a carer disutility in the model is not appropriate**

3.14 The company's submission included a disutility value applied to the model to account for the impact on carers and families of people with treatment-resistant depression. This was done by applying a disutility to the major depressive episode health state as the difference in utility between carers of patients with symptomatic treatment-resistant depression and carers of patients with treatment-resistant depression in remission. The ERG noted that this implied that carers of all patients in the major depressive episode health state would otherwise experience the utility associated with being in remission. The ERG argued that a methodologically better way to estimate disutility associated with a given state is to subtract the utility of that state from the utility associated with full health. The ERG applied a lower value to the disutility by using this different method to calculate the utility values. The committee acknowledged that there is an impact on the families and carers of people with treatment-resistant depression and considered the scenarios presented by the company and ERG. However, the committee considered that there was uncertainty about the appropriateness of including a carer disutility because of the lack of data on the direct effect on carers of people with treatment-resistant depression. It is also noted the lack of evidence on any direct benefit to carers after treatment with esketamine. The committee also noted that adjusting for carer disutility was not part of any other NICE technology appraisals in mental health and may lead to inequities across disease areas. The committee acknowledged the potential for an effect on carers but given the uncertainty over the evidence, the committee did not accept a carer disutility as part of the base case but considered it as a scenario and this did not change the committee's decision.



## **Resource use**

### **The cost of a course of esketamine treatment may be underestimated**

3.15 The ERG confirmed that the dose of esketamine used in the model was an average from the trial evidence. The committee was concerned that it was unclear what proportion of people received the 56 mg or the 84 mg doses and that no dose response curve was presented. It also considered that the company model did not fully account for a scenario in which a greater proportion of people receive the more expensive 84 mg dose, or the proportion who would receive the dose once weekly compared with once every 2 weeks. The committee concluded that the model may underestimate the cost of a course of esketamine treatment. The committee would like to see evidence of the proportions of people on each dose and frequencies of administrations, and scenarios exploring the effects of these assumptions on the cost-effectiveness results.

### **A range of ICERs is needed to estimate resource use costs associated with administering esketamine**

3.16 In its model, the company assumed a ratio of 2 nurses to 6 patients during the administration of esketamine and 1 nurse to 6 patients during the post-administration monitoring. The ERG preferred to model a 1:1 ratio throughout administration and monitoring because it considered this to be the most plausible in clinical practice. The NHS commissioning expert noted that because esketamine is a schedule 2 drug, it requires 2 healthcare professionals during part of the administration stage and it's subject to the full controlled drug requirements relating to prescriptions and storage. However, it may be reasonable to have a ratio of 1 nurse to 6 patients during the monitoring of esketamine. The clinical expert suggested that a ratio of 1:1 or 1:2 may be necessary when the service first starts, but that the ratio may increase to one nurse to a group of patients once the service becomes experienced and established. The patient expert, who was receiving treatment one to one, said that building a relationship with the healthcare professional was an important

component for treatment and recovery. The company clarified that their model included a band 5 and a band 4 nurse to administer esketamine and a band 5 nurse for post-administration monitoring. The committee considered that more additional training or more experienced nurses may be needed to manage the dissociative effects of esketamine. The committee concluded that the company's model may have underestimated the nurse experience required to safely administer, monitor and manage people receiving esketamine. The committee also concluded that, without further evidence, incremental cost-effectiveness ratios (ICERs) should be estimated based on nurse to patient ratios across a range from 1:1 to 1:6 during the monitoring phase of administration.

### **Significant investment will be needed to adopt esketamine into clinical practice**

3.17 The NHS commissioning expert advised that esketamine would require a significant investment to become part of NHS clinical practice. The committee heard that adopting esketamine would result in displacement of other mental health treatments because of its cost. The NHS commissioning expert was also concerned that implementation is unlikely within 90 days if esketamine was approved for use in the NHS because the structure and delivery of services would need to be changed. The commissioning expert said a potentially reasonable time to implement esketamine in a community setting is 12 months, and 6 months in a secondary hospital clinic setting. The staff training to administer and monitor esketamine may not have been accounted for in the model because additional training is needed to manage dissociative effects. The clinical expert suggested that it may be possible for some existing ECT suites to be used, but that their availability would vary across the country. The committee acknowledged that introducing esketamine would probably represent a change in managing people with treatment-resistant depression in the NHS. The committee considered that ECT is delivered in the most similar setting. The committee noted the results of a survey

conducted by the company which found that 18% of NHS Trusts had no specific plans on how they would adopt esketamine treatment. Therefore, the committee considered that some infrastructure costs may not be captured in the model. The committee acknowledged that the time needed to implement esketamine was unclear but that it is likely to be at least 6 months. The committee noted that NICE's [Guide to the methods of technology appraisal 2013](#) (section 5.5.8) states that if introduction of the technology requires changes in infrastructure, costs or savings should be included in the analysis. In addition, it also states (in section 6.2.14) that the 'committee will want to be increasingly certain of the cost effectiveness of a technology as the impact of the adoption of the technology on NHS resources increases'. The committee concluded that esketamine would require significant investment in costs and time to adopt and implement in NHS services.

### ***Cost-effectiveness estimate***

#### **There are several uncertainties associated with the cost-effectiveness estimates**

- 3.18 The committee noted the substantial uncertainties in the model inputs, specifically:
- Current clinical pathway includes different treatments (see section 3.3)
  - the unclear effect of psychological therapy on esketamine (see section 3.5)
  - Company did not provide evidence comparing esketamine with all relevant comparators (see section 3.4)
  - the significant uncertainty in the esketamine evidence (see sections 3.6 and 3.7)
  - the cost of esketamine may be underestimated because of uncertainty about the duration of treatment costs (see section 3.10), costs associated with repeat courses of treatment (see section 3.11), and dose frequency (see section 3.15).

The committee concluded that these uncertainties are unlikely to be resolved in the cost-effectiveness modelling. The committee also noted the significant investment required to adopt esketamine (see section 3.17). In line with [section 6.2.14 of the NICE guide to the methods of technology appraisal](#), the committee took into account the uncertainties in the evidence base when making its decision.

### **Esketamine is unlikely to be cost effective for treatment-resistant depression**

3.19 The company's base case included the following assumptions:

- a time horizon of 5 years
- adjustment for placebo effect to the acute response or remission transition probabilities only for the comparator
- discontinuation for reasons other than loss of efficacy for esketamine
- an effect on mortality for esketamine
- the cost of a clinic visit for esketamine based on a nurse to patient ratio of 1:6
- a carer disutility.

The company's base-case ICER for esketamine plus oral antidepressant compared with placebo plus oral antidepressant was £7,389 per QALY gained.

The committee's preferred modelling assumptions were reflected in the ERG's base-case analysis:

- a time horizon of 20 years
- no adjustment for placebo effect
- no discontinuation by 2 years for reasons other than loss of efficacy
- no effect on mortality for esketamine
- the cost of a clinic visit for esketamine based on a nurse to patient ratio with a range from 1:1 to 1:6
- no carer disutility.

The committee amended the ERG's assumption on the cost of clinic visits by adding a range for the nurse to patient ratio. The ERG had assumed a ratio of 1:1 in their base case.

The ERG's ICER using the committee's preferred assumptions was a range from £55,027 to £62,078 per QALY gained for 1:6 and 1:1 nurse to patient ratio respectively. The committee noted that the ERG's base case may not have covered all the committee concerns about dose frequency and infrastructure changes, which could substantially increase costs. The committee concluded that the most plausible cost-effectiveness estimate for esketamine was above the range usually considered a cost-effective use of NHS resources (see [NICE's guide to the methods of technology appraisal](#)).

### ***Other factors***

#### **There are no equalities issues that can be addressed in the guidance**

3.20 The company, patient organisation and the ERG highlighted that, because esketamine nasal spray requires attendance and monitoring at a clinic, geographic access may be an equalities consideration. However, the committee's recommendation does not restrict access to treatment for this group over other populations and so the committee agreed that this does not represent a potential equality issue. The commissioning expert raised considerations about equity of access for people in the criminal justice system. The committee considered that the recommendations do not prevent access to esketamine in the criminal justice system over any other setting. It understood that there were likely to be existing processes in place for managing controlled substances in the criminal justice system which would not prevent access to esketamine were it recommended. The patient expert raised considerations about people with additional physical health conditions who may need additional support when accessing treatment. Also, the patient organisation noted that some groups of people may have difficulties self-administering treatment or attending a clinic.

However, the committee's recommendation does not restrict access to treatment for this group over other populations and so the committee agreed that this does not represent a potential equality issue. The patient organisation raised that there may be cultural or religious objections to treatment with esketamine. However, these objections would apply to both treatment arms; the committee agreed that this does not represent a potential equality issue. The technical team also noted that the main trials only include people aged 18 to 64. However, any recommendation would extend to all adults and additional evidence from a trial that included adults aged over 64 was considered from the supplementary evidence.

## ***Conclusion***

### **Esketamine is not recommended**

3.21 Esketamine is not recommended for use in the NHS, within its marketing authorisation, for treating treatment-resistant depression. Despite taking into account the unmet need for effective treatment options for this population and the committee's most plausible assumptions, the costs and benefits of esketamine were very uncertain and the ICERs for the comparisons with placebo plus oral antidepressant were much higher than what is considered to be a cost-effective use of NHS resources. Therefore, the committee could not recommend esketamine for treating treatment-resistant depression.

## **4 Proposed date for review of guidance**

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh  
Chair, appraisal committee  
January 2020

## **5 Appraisal committee members and NICE project team**

### ***Appraisal committee members***

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee D](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### ***NICE project team***

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

#### **Omar Moreea**

Technical lead

#### **Lucy Beggs**

Technical adviser

#### **Gemma Barnacle**

Project manager

ISBN: [to be added at publication]