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?

Issue date: August 2020

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: 25 September 2020

Third 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 a 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 for treatment-resistant depression includes oral antidepressants, which are sometimes used with antipsychotic drugs. Electroconvulsive therapy can be used if oral treatments do not work. Esketamine is a nasal spray taken with an SSRI or an SNRI. The person having esketamine must be supervised by a healthcare professional in a clinic.

Clinical trials suggest that esketamine with an SSRI or SNRI may be more effective than placebo with an SSRI or SNRI. But it is unclear how effective esketamine is because of the way the trials were done. Also, people who may have esketamine in the NHS might have more severe depression than people in the trials.

There are problems with the economic model because it does not reflect how treatment-resistant depression is treated in the NHS or how long an episode of depression lasts. There is also uncertainty about:

- whether any improvements in symptoms continue after treatment stops and if this will improve someone's quality of life
- the costs of repeated courses of treatment with esketamine

- the costs of setting up treatment clinics, including how many nurses would be needed and making sure esketamine is subject to controlled drug requirements.

Taking this uncertainty into account, the cost-effectiveness estimates for esketamine are much higher than what NICE considers 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 The dosage schedule for esketamine is available in the summary of product characteristics.

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. Costs may vary in different settings because of negotiated procurement discounts. After consultation, the company proposed a confidential patient access scheme discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Janssen, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee met in January 2020 and made the decision not to recommend esketamine with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI) within its marketing authorisation.

The committee received many consultation comments based on different opinions of how to characterise treatment-resistant depression. It considered all comments objectively and in the context of the clinical trial evidence and economic modelling.

In its meeting in August 2020, the committee discussed the following issues, which were highlighted as new issues in the comments or included as responses to the first appraisal consultation document.

The condition and current treatment

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

3.1 The patient experts explained that treatment-resistant depression has a significant burden on all aspects of life, with a range of symptoms. The patient experts 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 the lives of children of people with treatment-resistant depression are also affected. 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 experts 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 experts highlighted that, when multiple courses of treatment do not work, the feelings of hopelessness get worse. They added that this was an inherent aspect of the 'treatment-resistant' nature of the condition. A patient expert who had recovered from treatment-resistant depression emphasised the importance of independence and return of character upon remission. The committee concluded that the effectiveness of current treatments for treatment-resistant depression is limited and that there is an unmet need for new treatment options.

Treatment pathway and comparator

Current clinical practice includes several different types of treatment

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 (when an antidepressant is used with a non-antidepressant), for example, an antidepressant with lithium or an antidepressant with an antipsychotic treatment
- combination therapy (an antidepressant with another antidepressant)
- electroconvulsive therapy (ECT).

The NICE guideline on depression also includes cognitive behavioural therapy (CBT) and other psychological therapies as options combined with the above treatments. However, the company noted that the

treatment pathway in clinical practice is different to the guideline. The clinical expert explained that the treatment pathway for treatment-resistant depression can vary between services across the UK. The clinical expert explained that, in general, most people with treatment-resistant depression have 3 to 4 standard oral antidepressant treatments from their GP. Only a small proportion (company estimate of 9.6%) are referred to a psychiatrist. Then, the first treatment choice is normally to optimise the dose of oral antidepressant or switch to a new oral treatment. Then 1 or 2 trials of augmentation therapy, with an antipsychotic drug or lithium combination therapy, would be considered before ECT. The committee acknowledged that the summary of product characteristics (SPC) states that esketamine must be prescribed by a psychiatrist. People who have been referred to a psychiatrist are likely to be at risk of suicide or whose symptoms have not responded to any treatments for an extended period. The committee concluded that the NICE guideline on depression may not represent clinical practice and multiple further lines of treatment are considered for treatment-resistant depression.

Esketamine is likely to be used later in the treatment pathway because it has a higher treatment burden than other treatments

3.4 The clinical expert explained that esketamine has a higher treatment burden than oral therapies. A person having esketamine would have to attend hospital or a suitable community health centre site twice a week and then weekly for some time, for approximately 2 hours or more each visit. Travel to and from the hospital may be difficult because it is not possible to drive after taking esketamine. So, carer support may be needed. Treatment-resistant depression is characterised by a lack of energy and motivation so this may not suit all people. For these reasons, the clinical expert considered that esketamine would be used later in the treatment pathway than it was in the clinical evidence, for depression that is more severe and more treatment resistant. The committee concluded that the treatment burden, combined with the safety concerns (see section

3.16), would mean esketamine is used later in the treatment pathway. This would be after 1 or 2 augmentation therapies have been trialled.

Placebo with oral antidepressants, as measured in the trials, is the most relevant comparator because the evidence for other treatments is highly uncertain

3.5 The company submission included oral antidepressants as comparators, stating that these were the most common oral treatments for the condition. A newly started oral antidepressant was used as the control arm in the trials (see section 3.7). The clinical experts highlighted that it does not reflect clinical practice to start a new oral antidepressant at the same time as esketamine. The committee noted that different treatments are used at different times and that esketamine may be used later in the treatment pathway (see section 3.3 and section 3.4). The clinical expert noted that esketamine may be used as a preferable alternative to ECT. However, consultees also commented that ECT would most often be had by people who are more acutely unwell and whose depression may have psychotic features, but esketamine would be contraindicated in these situations. The company provided a network meta-analysis of esketamine compared with all comparators for the acute phase of treatment. However, the company noted substantial heterogeneity of the study design, inclusion criteria and time of outcome measurement, which made the results unreliable. The ERG added that the network meta-analysis only used adjusted effects for the oral antidepressant with placebo arm of esketamine, which the ERG considered to be an incorrect assumption (see section 3.15). The committee concluded that the results comparing esketamine with some of the relevant comparators listed in the scope, such as combination or augmentation therapy and ECT, were highly uncertain. So, it considered only the results from the trials. These compared esketamine with oral antidepressants with placebo with oral antidepressants, even though these will not be the only comparators in clinical practice.

The effect of psychological therapy with drug treatments is an unresolvable uncertainty

3.6 The patient expert explained that psychological therapy can help with developing coping strategies and alleviate cognitive symptoms. An expert from the NICE guideline on depression noted that psychological therapies were not included as comparators or with combination treatments in the company's submission, but were included in the NICE appraisal scope. The clinical expert explained that CBT is used with drug treatment to treat depression, but not all people with depression can effectively engage with CBT because of the severity of their physical and cognitive symptoms. A patient expert suggested that treatment with esketamine may improve symptoms for enough time for people to engage with CBT. But 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. The company clarified that people taking esketamine can have psychological therapy on a different day but not at the same time as esketamine at their clinic visits. At consultation, some consultees commented that there is limited evidence for efficacy of psychotherapies in the treatment-resistant population and that including psychological therapies was not considered for other pharmacological interventions. The committee concluded that psychological therapies are an adjunctive therapy and a relevant part of the treatment pathway, but that its effect would likely be variable depending on the treatment population and severity of depressive symptoms (see section 3.4). But it considered the effect of combining psychological therapies with esketamine treatment to be an unresolvable uncertainty with the evidence available.

Clinical effectiveness

The clinical effectiveness evidence comes from 2 randomised controlled trials

3.7 The company's clinical effectiveness evidence came from 2 randomised, double-blind, parallel-group, active-controlled, phase 3 trials, TRANSFORM-2 and SUSTAIN-1. The trials compared

- a flexible dose of esketamine with oral antidepressant and
- placebo with oral antidepressant

in adults aged 18 to 64 with treatment-resistant depression. TRANSFORM-2 provided randomised evidence for the acute phase of treatment for the 4-week induction phase of the study, measuring symptom response and remission rates. SUSTAIN-1 provided randomised evidence in the longer term through continuation and maintenance of treatment, measuring symptom relapse rates. People could participate in SUSTAIN-1 as new participants or they could transfer from TRANSFORM-1 or TRANSFORM-2 if depression was in stable remission or stable response. 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). Evidence for acute treatment of depression in people aged 65 and over came from TRANSFORM-3, although this included a lower starting dose, as in the SPC. The committee noted that TRANSFORM-1 and TRANSFORM-3 did not show significant improvements in outcomes for esketamine with oral antidepressant compared with oral antidepressant with placebo.

MADRS is used to measure depression severity and effect of treatment

3.8 The Montgomery-Asberg Depression Rating Scale (MADRS) measures severity of depression. It is scored between 0 and 60, 0 meaning no depressive symptoms. Primary outcomes of response and remission in TRANSFORM-2 and relapse rates in SUSTAIN-1 were measured using MADRS. Moderate to severe depression was defined in TRANSFORM-2

as a MADRS score of 28 or more and the mean baseline MADRS score of the participants was around 37. Symptom response was defined as a reduction in score of 50% or more from baseline. The clinical expert explained that this is a standard criterion for response. Remission was defined as a MADRS score of 12 or less with minimal or no symptoms. The clinical expert considered that remission is normally measured by a MADRS score of 10 or less (as in NICE technology appraisal guidance on vortioxetine) but that this would not substantially affect the results. Relapse was defined as a MADRS score of 22 or more for 2 consecutive assessments or other clinically relevant event such as hospitalisation for depression. Recovery was defined as symptoms remaining in remission for about 9 months and recurrence was defined as depression relapsing after recovery. The clinical expert noted that MADRS is non-linear, meaning that a change in score at the lower end of the scale does not mean the same, in terms of clinical importance, as a change in score at higher end of the scale. The committee noted that remission and relapse are fixed to MADRS, but response measurement depends on the score at baseline, which complicates interpretation. The committee also noted that the score used for relapse was not equivalent to the MADRS score for moderate to severe depression, which affected the health state utility values and transitions in the economic model (see section 3.21 and section 3.23). The committee took this into account in its decision-making.

The response and remission evidence from TRANSFORM-2 should be considered with caution because of the short duration of the trial

3.9 TRANSFORM-2 measured a statistically significant difference between esketamine nasal spray with newly started oral antidepressant compared with oral antidepressant with placebo after 28 days. The reduction in MADRS score from baseline was 21 for esketamine and 17 for placebo. The committee noted a separation of treatment effect after 2 days (or 1 treatment), which remained for the duration of the 4 weeks. The committee considered that this may not be a true effect on depressive symptoms. A consultee commented that the 4-week duration of the trial

has 'little bearing on the treatment for depression'. The committee noted that the NICE guideline on depression recommended an initial assessment at 2 to 4 weeks to assess symptom response to oral antidepressant, but further regular assessments and dose optimisation would be considered after this point. The committee considered that the data still showed a downward trend in MADRS score, with no evidence of flattening, so 4 weeks was not an appropriate endpoint for measuring response and remission for both treatments. Also, a consultee commented that splitting data into 2 groups, response or remission and no response or remission, can lead to an overestimation of differences between arms. The committee acknowledged that splitting the data into 2 groups could have inflated the differences between arms, particularly because the mean reduction in MADRS was near to the threshold for response in both arms at day 28. So, people could meet the criterion for symptom response in 1 arm but only have minimal differences in MADRS score in the other arm. The committee concluded the response and remission evidence from TRANSFORM-2 should be considered with caution because of the duration of the trial.

The TRANSFORM-2 study is not powered to detect difference in effect between treatment arms so could show a false positive result

3.10 TRANSFORM-2 showed a 4-point difference between treatment arms on the MADRS scale (see section 3.9). A consultee commented that this was not a clinically significant difference because a minimally improved score of 7 to 9 would be expected to establish clinical benefit for an individual person. The clinical expert commented that for a population in a trial, a mean difference of 4 was clinically significant. The treatment effect of the control arm was greater than would be expected in other trials in depression (see section 3.15). Also, the mean 4-point difference in MADRS score was much smaller than the total effect of the placebo and antidepressant arm, which saw a reduction in MADRS score of 17. The committee noted that there is debate about what is considered a minimal clinically significant difference in the literature. The committee considered

that it is difficult to distinguish the following issues from the true difference in treatment effect:

- the effect of starting a new oral antidepressant at the same time as esketamine
- the trial designs and inclusion criteria leading to a much higher placebo response than would be expected (see section 3.15) which could affect relative treatment effect
- the non-linearity of MADRS (see section 3.8)
- a likely regression to the mean because patients were recruited during the peak of a depressive episode
- early 4-week assessment of outcomes (see section 3.9)

The committee considered there to be differing opinions on the importance of the observed difference but noted the European Medicines Agency (EMA) considered the effect size to be clinically significant. However, the committee also noted that all the TRANSFORM studies used a difference in MADRS score of 6.5 in the power calculations used to estimate sample sizes. The committee concluded that TRANSFORM-2 was not powered to detect a difference of 4 points on MADRS and could potentially have shown a false positive result.

The withdrawal design of SUSTAIN-1 could bias the relapse outcomes in favour of esketamine

3.11 SUSTAIN-1 measured withdrawal of esketamine for a randomised population of people whose depression was in stable response or stable remission. The ERG commented that there was potential for selection bias using these criteria. This is because if esketamine is tolerated participants who have the drug for 16 weeks and do not stop (induction and optimisation phases) stay in the trial by design, which selects people who are less likely to be affected by the treatment burden and do not have adverse events that make them stop treatment. After the optimisation phase, randomised participants stopped having esketamine nasal spray and instead had placebo. All participants continued to have oral

antidepressant. A consultee commented that there is potential for functional unblinding with this design because participants randomised to placebo may notice the absence of psychoactive effects. The consequent negative expectations could increase the chance of relapse. The committee understood from consultation that relapses are highest in the first 4 weeks after stopping an active treatment such as esketamine, and this could be consistent with potential unblinding. The clinical expert commented that the number of relapses could have been overestimated. The committee also noted that people with depression in stable response or remission from the TRANSFORM trials who only had placebo had a lower relapse rate than those who stopped esketamine, although this was not explored fully by the company. The committee concluded that the withdrawal design of SUSTAIN-1 may have biased results in favour of esketamine, if patients were unblinded to what treatment they were having.

Withdrawal effects are difficult to distinguish from symptoms of depression

3.12 After the first committee meeting, the committee noted that the company had not provided evidence on the effects of withdrawal from esketamine. At consultation a consultee considered that the potential adverse withdrawal effects of esketamine could have confounded the relapse rates of SUSTAIN-1. This was because MADRS is very similar to scales used to measure withdrawal, such as the Physician Withdrawal Checklist (PWC-20). The company considered that there would be no long-term withdrawal effects of esketamine because at this dose it leaves the body quickly. However, the company also did not use data from SUSTAIN-1 for relapse rate in the oral antidepressant with placebo arm in the economic model to avoid any withdrawal effect (see section 3.21). The clinical expert explained that withdrawal effects of ketamine seen in recreational use are from higher doses. Physical responses, such as sweating and shaking, are not expected at this level of dose. The committee noted that anxiety increased in some participants in SUSTAIN-1, 2 weeks after stopping esketamine for both arms, as measured by the PWC-20. The

committee concluded that any withdrawal effect would be difficult to distinguish from a change in depressive symptoms because withdrawal is likely to adversely affect people psychologically, including potential increased feelings of hopelessness (see section 3.2).

The differences in relapse rate in the SUSTAIN-1 trial data should be considered with caution

3.13 The SUSTAIN-1 trial was done in multiple sites around the world with different numbers of participants in each site. A consultee commented that 1 site in Poland was an outlier. This was because it had a very high relapse rate in the oral antidepressant with placebo arm (16 out of 16 relapses) compared with fewer relapses in the esketamine with oral antidepressant arm (2 out of 9 relapses). The EMA did not find any reason to exclude data from the site in Poland. The committee did not consider it appropriate to exclude this site because it was included by the EMA, although it noted that the results of SUSTAIN-1 should be considered with caution.

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

3.14 The company assumed that data from TRANSFORM-2 and SUSTAIN-1 were generalisable to NHS clinical practice but no patients were recruited in the UK. 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
- with depression that 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 those excluded from TRANSFORM-2 and SUSTAIN-1 could represent a substantial proportion of people with treatment-resistant depression. It considered that excluding these people limited the

generalisability of the trials. The expert from the NICE guideline on depression 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. A clinical expert also noted that excluding suicide risk was a concern because suicidal ideation is often an integral part of the disease. The committee noted that many people referred to a psychiatrist (a requirement of the SPC) in NHS clinical practice would be at higher risk of suicide. The clinical experts acknowledged the limitations of the other exclusions but explained that the exclusion criteria are standard for trials in this population. Comments received at consultation confirmed that uncertainty introduced by excluding these patients is common in trials in this disease area. The company explained 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 people with psychiatric comorbidities take esketamine. The committee also noted that the population in the trial may not be in line with its expected clinical use (see section 3.4) and that patients with more severe symptoms may be more likely to be excluded using these criteria. The committee considered that the other exclusion criteria could inhibit the generalisability of the trial results but that this was an unresolvable uncertainty in this disease area with currently available data. The committee concluded that excluding people with recent suicidal ideation limits the generalisability of the trials to the NHS for people with treatment-resistant depression.

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

3.15 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 of any or all of the following points:

- people visited the clinic more than in clinical practice
- symptoms respond to the novelty of a nasal spray treatment
- people have a high expectation of esketamine
- symptoms respond to the new oral antidepressant given alongside placebo.

The company considered that all 4 factors would be present in esketamine treatment in clinical practice but only the new 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:

- Blinding was an issue in the trials (see section 3.11) and when people having treatment do not have dissociative effects, they may realise they are not having esketamine. This would reduce the potential effect of treatment expectation and response to the novel way esketamine is used.
- 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 esketamine. The ERG considered that any adjustment likely would overestimate the effect of esketamine treatment and would create a bias in its favour. The expert from the NICE guideline on depression 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 committee concluded that the trial design accounts for placebo effect already, and that adjustment was not appropriate because of the risk of bias.

- In the trial, the placebo arm had 6 more clinical visits than would be expected in clinical practice. The company 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. The committee considered that the additional clinical contact involved in administering esketamine included support from mental health nurses and establishing relationships, which could be an integral part of treatment (see section 3.29). The committee noted that planned and structured clinical contact improves outcomes and that in NHS practice oral antidepressant treatment is ideally combined with CBT. 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 3.6), 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.

Taking the above points into account, the committee concluded that it was not appropriate to adjust the efficacy estimates of the placebo arm in the trials.

Safety

Safety must be considered when administering and monitoring esketamine

3.16 The EMA identified some risks of esketamine use in the SPC. These included drug abuse, transient dissociative states and perception disorders, disturbances in consciousness, and increased blood pressure. At the first meeting, a registry was suggested to monitor how much

esketamine a person has and to prevent people from getting esketamine from more than one source. The clinical expert also suggested including IV ketamine on this registry for the same reasons. They explained that there is likely to be an increased risk of misuse or abuse in people who are dependent on alcohol and drugs. The NHS commissioning expert explained that, because esketamine is a schedule 2 drug, it is subject to the full controlled drug requirements relating to prescriptions and storage (see section 3.30). The committee acknowledged that the monitoring period would likely mitigate the other risks identified in the risk management plan and the committee did not need to consider these further. However, it noted that a registry must be considered when administering and monitoring esketamine to prevent abuse and misuse. After consultation, the committee received further comments about the safety of esketamine. Namely, that the clinical evidence showed there were 3 suicides in people that stopped esketamine in a population who had no recent suicidal ideation or behaviour. There were no suicides in people who had placebo, although people had placebo for less time. In SUSTAIN-1, there were also a higher number of hospitalisations and clinically relevant events. The committee recognised the numbers reported were very small but enough to doubt that there would be more crisis hospitalisation for placebo than esketamine. It concluded that the precautions in the SPC were appropriate regarding risk of suicide and management through increased monitoring, particularly during early treatment and after dose changes.

Economic model

The company's economic model does not reflect the course of the disease

3.17 The company economic model consisted of 5 health states: major depressive episode (MDE), response, remission, recovery and death. The transitions between each health state were determined by the relapse, remission and response rates in TRANSFORM-2, SUSTAIN-1 (see section 3.8) and values in the literature, for example the STAR*D trial (a

large-scale clinical trial for people with depression). All people start in the MDE state and the initial treatment uses response and remission data from TRANSFORM-2. This is followed by 3 more potential subsequent treatments after non-response or relapse, and then a non-specified mixture of treatments. The model output suggests that within 1 year, 78% of people with treatment-resistant depression in current clinical practice do not have symptom response to any treatments long-term. So, they then occupy the MDE state for the remainder of the time horizon. At consultation, a consultee stated that improvements in depression are generally maintained at the end of acute treatment, and on average symptoms improve further. Another consultee considered that depression can be highly episodic, with a good success rate when people adhere to treatment. The committee heard that there is minimal long-term outcome data for people with treatment-resistant depression. One study in a tertiary care setting (inpatients) suggested that half of people are in remission at a median of 3 years follow-up. This population would have more severe depression than people with treatment-resistant depression in the clinical evidence. The clinical expert estimated that currently 20% to 30% of people with treatment-resistant depression have chronic longer-term disease that has not responded to any treatment. The committee considered that the economic model likely overestimated the number of people in the MDE health state in both treatment arms. The ERG noted that this was likely because subsequent treatment effects had been underestimated (see section 3.18) and modelling a high relapse and recurrence rate (see section 3.21). The committee also considered that the health states used in the model were not the most appropriate for the economic modelling. This was because it was likely there was heterogeneity of costs and utility within these health states. The committee concluded that the economic model did not reflect the course of the disease and does not reflect the episodic nature of the condition.

The effect of subsequent treatments is underestimated and the ERG's adjustment is more plausible

3.18 The ERG noted that the response and remission rates of subsequent treatments were likely to be underestimated. The company stated that these rates were calculated by adjusting the STAR*D data for subsequent treatments to the SUSTAIN-1 population. The ERG was unable to validate how the subsequent treatments were calculated but considered them to be considerably lower than the observed response and remission rates in STAR*D. Also, the response and remission rates were calculated on a 4-weekly basis to be implemented per cycle in the model. The model structure meant symptoms had to respond within 4 weeks or people would have the next treatment. The extremely low response and remission rates of subsequent treatments and the model structure meant that most patients whose symptoms did not respond to the first treatment had 3 lines of subsequent treatment within 12 weeks that did not work. The committee considered that this would not reflect clinical practice. The ERG provided a scenario that reduced response and remission rates proportionally by each line of therapy, using the ratio measured in the STAR*D trial between the third and fourth line treatments. The ERG noted that this was consistent with the committee preference for proportional reduction in the NICE technology appraisal guidance on vortioxetine. The committee concluded that the output of the ERG model was more clinically plausible than the company base case, but still did not accurately capture the course of the disease.

A 20-year time horizon for the economic model is preferred

3.19 Treatment-resistant depression is an episodic condition and the company 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, so it preferred a 20-year time horizon. The committee considered 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 (particularly for 20% to 30% of people whose symptoms do not respond to any treatment currently) so a longer time horizon was appropriate. The expert from the NICE guideline on depression agreed that a longer time horizon was needed to account for the duration of the condition and the need for any subsequent treatments. The committee noted uncertainty about long-term outcomes (see section 3.17) but concluded that a shorter time horizon may not solve this issue.

The company's approach to including repeat treatment with esketamine in the current model is not appropriate

3.20 At the first committee meeting, the ERG highlighted that the company's model structure did not allow for any repeat courses of esketamine. But it did allow for major depressive disorder recurrence after a specified period when depression was in stable remission. The patient expert suggested that if treatment with esketamine worked for someone then they would consider having the treatment again when symptoms returned. The clinical expert agreed that the best indicator for what treatment would work would be what depression had responded to previously. The committee had not seen any evidence for the repeated use of esketamine but considered it plausible and would like to explore it further with scenario analysis. After consultation, the company provided a model with an option for repeat treatment that increased the cost effectiveness of esketamine. But it noted that the assumptions about efficacy on further treatment increased the uncertainty of the results. The committee considered that the company's model greatly overestimated the number of people whose depression would relapse and enter the MDE state (see section 3.17) so would need repeat treatment. So, the committee concluded that any repeat treatment analysis would be flawed with the current model estimates. The committee also acknowledged that there were no data to inform outcomes for people who have repeat treatment. It

recognised that the company's preference to model 1 line of esketamine treatment may be the most informative, despite the committee's preference for a longer time horizon. The committee concluded that the company's approach of modelling repeat treatment was not appropriate with the current evidence.

The transitions between different health states contribute to the model's uncertainty

3.21 The committee highlighted that the transitions between some health states were uncertain because of the trial design and the effects of including other trial data. This was because:

- The transition between remission or response to MDE may have been overestimated. This is because the relapse and loss of response rates for esketamine with oral antidepressant are based on a MADRS score of more than 22. But, the MDE health state is based on a MADRS score of 28 of more (see section 3.8).
- The relapse and loss of response rates for the oral antidepressant arm were sourced from the STAR*D trial. The STAR*D trial used different relapse criteria. Also, it was unclear if the population from STAR*D is generalisable to the NHS.
- The transitions between response and remission states were also sourced from STAR*D for both arms, although this assumption was not fully explored by the company. The criteria for these transitions are unclear because response is calculated as a change from baseline rather than measured using a specific MADRS range (see section 3.8) and STAR*D used different criteria to measure both response and remission.
- The recurrence rate is modelled as a flat rate for both treatments based on the number of people in both arms whose depression relapsed after 9 months of successful treatment. The committee considered this to overestimate recurrence (see section 3.8). Recurrence was also

applied per cycle throughout the model time horizon, so there was no option of permanent recovery.

The committee concluded these transitions may have contributed to the high number of people in the MDE state, which contributed to the uncertainty of the model.

It is not appropriate to include an effect of esketamine on mortality in the model

3.22 In its economic model, the company assumed there were 2 risks for dying: 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). This indirectly decreased the risk of excess mortality with esketamine. The committee considered it plausible that esketamine could affect mortality. It considered that excess mortality was only applied in the MDE health state, which was overpopulated in the economic model (see section 3.17). Because of this, issues with generalisability, excluding people with an acute suicide risk (see section 3.14) and the lack of data, the committee concluded it could not accept a reduced suicide, or mortality, risk.

Utility values

The difference in utility values between health states is likely overestimated

3.23 The company measured utility in the TRANSFORM-2 and SUSTAIN-1 trials as EQ-5D-5L measurements and mapped these to EQ-5D-3L utility values as in the NICE reference case. These utility values were applied to the modelled health states (see section 3.17). The committee noted that the utility value for MDE of 0.417 was measured from the baseline utility scores in TRANSFORM-1 at a mean MADRS score of 37. However, the transition from relapse or remission to the MDE state needed a MADRS score of 22 or more for 2 consecutive measurements (see section 3.8). The committee noted that the mean EQ-5D-5L health score index was

consistently higher than 0.8 for all participants at the end of maintenance for SUSTAIN-1. In participants who were randomised to withdraw from esketamine, 45% of people whose depression was in stable remission and 58% of people whose depression was in stable response relapsed. The committee considered that this would not correspond to the relatively high EQ-5D-5L health score index above 0.8 if this represented a true transition to the MDE health state. The committee also noted that response criteria were not fixed to absolute MADRS values. This made interpreting the utility values difficult because these values could have come from people with MADRS scores of between 13 and a maximum value above the threshold for relapse of 22 or more. The committee concluded that the transition from response or remission to relapse was not modelled appropriately and likely overestimated the difference in utility value for people whose depression relapsed.

It is appropriate to consider applying a carer disutility in the model and to consider the effect without it

3.24 The company submission included a disutility value applied to the model for the effect of treatment-resistant depression on carers and families. This was done by applying a disutility to the MDE health state. This was the difference in utility between carers of people with symptomatic treatment-resistant depression and carers of people with treatment-resistant depression that was in remission. The ERG noted that this implied that carers of all people in the MDE health state would have a utility value associated with being in remission. The ERG argued that a methodologically better way to estimate disutility for a specific state is to subtract the utility of that state from the utility for full health. The ERG applied a lower value to the disutility by using this method to calculate the utility values. The committee acknowledged treatment-resistant depression has an effect on carers and families and considered the ERG scenario to be most appropriate. But it considered that there was uncertainty about how appropriate including a carer disutility was. This was because of the lack of data on the direct effect treatment-resistant

depression had on carers. The committee noted the lack of evidence on any direct benefit to carers after treatment with esketamine. It also noted the potential for an increased treatment burden for carers as well as people with depression (see section 3.2). The committee considered that carer utility is only applied in the MDE health state, which is overpopulated in the economic model (see section 3.17). It noted that carer disutility was not considered in NICE technology appraisal guidance on vortioxetine. The committee concluded that it was appropriate to consider scenarios with both the ERG carer disutility scenario and no carer disutility because the effect was uncertain.

Stopping treatment

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

3.25 The company assumed that some people would stop taking esketamine for reasons other than lack of efficacy, in line with the criteria in the SPC and additional guidance on stopping treatment. In the company model, stopping rates (for reasons other than lack of efficacy) for esketamine varied by treatment phase. Based on research questionnaires from clinicians, the company modelled that 52% of people whose depression was in stable remission would immediately stop treatment after 9 months, with 16% expected to continue treatment for more than 2 years. Stopping treatment was assumed to stop costs for esketamine incurring, but have no effect on QALYs. The ERG preferred to assume no immediate stopping and instead modelled a continued exponential reduction based on extrapolation of the trial data. This was because no evidence was submitted that showed the effect of stopping on symptoms or quality of life. The ERG and clinical experts also highlighted that there were no data to accurately determine stopping rates in clinical practice. The ERG noted that no data was collected for people who stopped treatment for reasons other than lack of efficacy, and the reasons why they stopped were not explored. In response to consultation, the company provided further

scenarios for stopping treatment including one where people stopped taking esketamine at a faster rate after 9 months, but no immediate stopping (scenario C in the company response to the first appraisal consultation document). It also provided some scenarios that explored a utility decrement after stopping treatment. The committee considered that the research data informing the company revised base case may not be generalisable to NHS practice because it classified patients into risk levels and applied these to the population in SUSTAIN-1. In NHS clinical practice, people would likely be at higher risk than in SUSTAIN-1 and circumstances for stopping treatment are very different in people who were not included in the trials (see section 3.4 and section 3.14). The committee also considered that it is possible more people's depression would respond to treatment, but not all of them would be in remission if their depression was more treatment resistant. These people would not stop treatment immediately at 9 months using the company's stopping criteria. The committee also noted that the data for the utility decrement came from the SUSTAIN-2 study and had limited use in the model because of the high proportion in the MDE state (see section 3.17), so did not explore this scenario further. The committee concluded that the scenario with a faster stopping rate after 9 months was the most clinically plausible, given the expected population. But estimating when people would stop treatment is highly uncertain without any data.

Stopping treatment in clinical practice would be based on people's individual circumstances

3.26 The clinical expert explained that stopping treatment is variable in clinical practice. They would expect that the decision to stop treatment would be made after a discussion of the person's individual circumstances. The clinical expert also considered that this could involve treatment pauses to assess how a person feels without esketamine. 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. The committee considered it likely that people would stop esketamine for other reasons over a 2-year period. This could include recovery, although there was no option for longer term recovery in the company model (see section 3.21). People could also stop esketamine because of the high treatment burden associated with it (see section 3.4). However, people who consider esketamine to be effective may also want to carry on taking the drug. The committee recognised that, in practice, people may have repeat courses of esketamine, but it increased uncertainty when this was included in the model (see section 3.20). The committee considered the additional stopping criteria introduced by the company. But it concluded that because of people's individual circumstances and preferences, stopping treatment would rarely be guided by these criteria. This would particularly be the case for the expected population in NHS clinical practice (see section 3.4).

Resource use

The cost of a course of esketamine treatment may be underestimated

3.27 The company confirmed that the dose of esketamine used in the model was an average from the trial evidence although the costs in the optimisation phase were still unclear. The committee was concerned that no dose response curve was presented. It also considered the following unclear:

- what proportion of people had the 56 mg or the 84 mg doses
- what proportion had treatment once weekly or every 2 weeks
- if people develop a tolerance to esketamine and need increased doses to achieve the same therapeutic effect.

The committee noted that a weekly dose compared with every 2 weeks relied on what was considered response to treatment (MADRS score of 12 or less or more than 12, see section 3.8). The committee considered that a change in what is considered response, for example a MADRS

score of 10 or less (as in NICE's technology appraisal guidance on vortioxetine), could affect the costs of treatment. Also, issues with generalisability of the trial evidence and esketamine's position in the treatment pathway (see sections 3.4 and section 3.14) could increase the number of people whose depression was considered to have only responded, compared with people with depression considered to be in remission. This could increase the costs substantially. The committee concluded that the model may underestimate the cost of a course of esketamine treatment. The committee would like to see the proportion of people having each dose, how often people have esketamine (weekly or every 2 weeks), reasons for the dosing choices and scenarios exploring the effects of these assumptions on the cost-effectiveness results.

Healthcare resource use costs should be made equal across both arms in the current model

3.28 The company modelled healthcare resource use by health state as defined in the economic model (see section 3.17). Resource use for each health state was measured using a retrospective review of patients in UK clinical practice. The committee noted the MDE health state was of great importance in the model because of the amount of time people were in this health state (see section 3.17). The retrospective review also showed most healthcare resource costs were accrued in the MDE health state, which included primary care visits, secondary care visits, psychological-based interventions, ECT, hospitalisations and crisis resolution home teams. The committee considered that CBT and ECT were excluded from the trials and should not be included in the medical costs. The committee noted that the data from SUSTAIN-1 showed a higher number of hospitalisations and clinically relevant events in people who had esketamine and the resource use associated with these events was not captured in the model. This was because costs of these events were not modelled explicitly (as adverse events) and all resource use was assumed to be related to health state. The committee noted that SUSTAIN-1 measured resource use but no scenarios were provided using any

resource use or event data from the trial. However, the committee considered it could be reasonable to estimate resource use from the retrospective review because SUSTAIN-1 was not powered to detect differences in clinical events and may not be generalisable to NHS resource use because it was an international trial. The committee was also unclear about the generalisability of the patient population and characterisation of health states in the retrospective review compared with the trial population and expected use in clinical practice. The committee noted some limitations of the retrospective review design and the potential for selection bias of patients that are seen more frequently. The costs of resource use contributed to almost all of the costs within the model for the placebo with oral antidepressant arm and about 72% of these costs came from hospitalisations and crisis resolution home teams. The committee considered that these costs were driven by events and that there is considerable uncertainty whether esketamine would reduce these events from the SUSTAIN-1 data. Because of this, and the importance of the overpopulated MDE health state, it concluded that it was most appropriate to make healthcare resource use costs equal across treatment arms. The committee did not consider this conservative because resource use of esketamine could be higher than placebo if using SUSTAIN-1 data, and there is considerable uncertainty with this assumption.

A 1 to 2 ratio of nurses to patients is an appropriate resource cost during post-administration monitoring

3.29 In its model, the company assumed a ratio of 2 nurses to 6 patients when esketamine is administered, and 1 nurse to 6 patients during monitoring after treatment. The ERG preferred to model a 1 to 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, 2 healthcare professionals must be present when it is administered. It is also 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 treatment. The clinical expert suggested that a ratio of 1 to 1 or 1 to 2 may be necessary when a service first starts administering esketamine, but that the ratio may increase to 1 nurse to a group of patients once the service becomes experienced and established although there could be logistical challenges in scheduling administration and monitoring with many patients at one time. The patient experts, who had treatment 1 to 1, said that building a relationship with the healthcare professional was an important part of treatment and recovery. The company clarified that their model included a band 5 and a band 4 nursing associate or healthcare assistant to administer esketamine and a band 5 nurse for monitoring. The committee considered that additional training or more experienced nurses may be needed to manage the dissociative effects of esketamine. The company said it would provide additional training however it was unclear whether costs would be covered for backfill of staff while undertaking training. The committee concluded that the company's model may have underestimated the nurse experience and time required to safely administer, monitor, and manage the dissociative effects of esketamine, and that a 1 to 2 ratio of nurses to patients was appropriate.

Significant investment will be needed to use esketamine in the NHS, but costs are difficult to quantify

3.30 The company did not include any costs of implementing esketamine in the economic model. This is because of the proposal to convert ECT suites to esketamine treatment centres (see section 3.31). It also said it would provide staff training to administer and monitor esketamine, needed to manage dissociative effects, at no additional cost. But the NHS commissioning expert considered there to be several costs for adopting esketamine:

- costs of conversion of ECT suites
- costs of medical equipment to monitor and manage any post-dose medical complications

- staff training to manage post-dose complications, including potential costs of recruitment if there are not enough staff currently available in practice
- costs associated with the controlled nature of the drug, including storage, transportation, disposal and adequate staffing and governance training
- costs associated with creating and managing a registry to avoid misuse and abuse of esketamine (see section 3.16).

The commissioning expert noted that these costs would be difficult to quantify. The committee also noted that the costs would depend on the expected population in clinical use (see section 3.4). 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 needs changes in infrastructure, costs or savings should be included in the analysis. So, the committee concluded that there would need to be significant investment to use esketamine in the NHS, but considered that these costs could be difficult to quantify.

It will take time and resource use for esketamine to become part of clinical practice

3.31 The NHS commissioning expert advised that there would need to be significant investment for esketamine to become part of NHS clinical practice. They noted that esketamine would displace other mental health treatments because of its cost. The company considered that ECT suites could be converted to administer esketamine with minimal resource use. It considered that esketamine would not take long to become part of NHS practice, quoting market research that showed 82% of NHS trusts have some plans for how they would use esketamine. The NHS commissioning expert considered that negotiating use of ECT suites may be complex for some trusts and not possible for others. They considered that it would be wrong to limit the availability of esketamine to those trusts that have an ECT suite that can be easily converted. The committee was aware of a potential equality issue (see section 3.34), and considered that

esketamine could be used in a community setting to enable easier access to treatment. The clinical expert noted that some trusts have large geographical areas and access would not be available for everyone. The NHS commissioning expert was concerned that, if esketamine was approved for use in the NHS, implementing it would be difficult within 90 days. This is because the structure and delivery of services would need to be changed. They said a reasonable time to implement esketamine in a community setting would be 12 months, and 6 months in a secondary hospital clinic setting. The committee noted that community settings may be unfamiliar with this treatment and the schedule 2 drug regulations required for its handling, which may need further investment to set up. The committee noted that NICE's Guide to the methods of technology appraisal 2013 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 were mindful of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 which states that if appropriate, NICE must specify a longer period of implementation if the health technology cannot be appropriately administered until training is, (ii) certain health service infrastructure requirements including goods, the materials or other facilities are, or (iii)other appropriate health services resources, including staff, are in place. It concluded that if esketamine was recommended the relevant commissioner for secondary hospital clinic services could need more than 6 months from guidance publication to implement the treatment. The relevant commissioner for a community setting could need more than 12 months.

Cost-effectiveness estimate

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

3.32 The company's revised base case after consultation gave an incremental cost-effectiveness ratio (ICER) of £10,790 per QALY gained for esketamine compared with oral antidepressants. This analysis used the list price for esketamine but the company also provided analyses including the patient access scheme discount, the results of which cannot be presented because of confidentiality. The revised base case included some of committee's preferred assumptions, including a time horizon of 20 years, no adjustment for placebo effect for acute response or remission transitions probabilities, and no excess effect of esketamine on mortality. The committee requested further analysis with its preferred modelling assumptions which included:

- the ERG's scenario for subsequent treatments (see section 3.18)
- no carer disutility and sensitivity analysis with the ERG's method of applying carer disutility (see section 3.24)
- the company scenario for stopping treatment that included an increased rate of stopping after 9 months on treatment (referred to as scenario C by the company, see section 3.25)
- costs associated with a ratio of 1 to 2 nurses to patients during the monitoring phase of treatment (see section 3.29)
- equalising the costs of resource use between esketamine with oral antidepressants and placebo with oral antidepressants (see section 3.28)

Using the committee's preferred assumptions, the ERG's ICER was in the range of £64,554 to £72,158 per QALY gained, including no carer disutility and the ERG's carer disutility, respectively. The committee noted that the ICER with its preferred assumptions did not cover all the concerns discussed at committee, including:

- the cost-effectiveness estimate being based on clinical evidence that does not represent the expected use of esketamine in NHS clinical practice (see section 3.4)
- uncertainties with the clinical evidence that inform the economic model and transitions between health states (see sections 3.7 to 3.13 and section 3.21)
- the clinical trial evidence not including people with recent suicidal behaviour, which limits the generalisability of the results (see section 3.14)
- if depression responds to esketamine but does not enter remission, this could be associated with much higher costs of esketamine because of stopping criteria (see section 3.25) and a more frequent dosing schedule (see section 3.27) than modelled
- the ERG's subsequent treatment scenario potentially not accurately capturing the course of the disease (see section 3.17)
- the substantial costs of adopting esketamine in clinical practice that have not been included in the model (see section 3.30).

The committee concluded that the most plausible cost-effectiveness estimate for esketamine was between £64,554 and £73,158 per QALY gained using the list price for esketamine. These ICERs were lower when the confidential patient access scheme was applied (results cannot be presented because of confidentiality) but were still substantially higher than what NICE considers a cost-effective use of NHS resources (see NICE's guide to the methods of technology appraisal)

Other factors

Esketamine is innovative because it has a novel biological mechanism

3.33 The company considers esketamine to be innovative because it represents a step change in the treatment of treatment-resistant depression. The company noted esketamine has a novel biological mechanism of action in a disease area that has not had a new mechanism for 30 years. A consultee commented that the fundamentally different

biological mechanism has caused great excitement among patients and clinicians. Also, esketamine is sprayed in the nose which means it works rapidly and is non-invasive compared to ECT. The committee concluded that the biological mechanism of esketamine could be innovative, but it was uncertain if it would be a step change in treatment because of the uncertainty of the clinical evidence.

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

3.34 The company, patient organisation and the ERG highlighted that, because esketamine nasal spray needs treatment be given and monitored at a clinic, geographical access may be an equalities consideration. The committee considered that symptoms of depression include lack of energy and motivation (see section 3.4), so it may be difficult for people to travel a long way to attend esketamine clinics. It considered that administering esketamine in a community setting would be necessary to ensure equity of access to treatment (see section 3.31). Also, the patient expert raised that people with physical health conditions may need additional support when accessing treatment, and the patient organisation noted that some groups of people may have difficulties self-administering treatment or attending a clinic. But because the committee's recommendation does not restrict access to treatment for some groups over others, the committee agreed these were not potential equalities issues. The NHS commissioning expert raised concerns 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 organisation raised that there may be cultural or religious objections to treatment with esketamine. The committee was aware that these objections would also apply for other existing treatments for depression; however it agreed that this equality issue could not be addressed in a recommendation. The technical team

also noted that the main clinical evidence only includes 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. So, the committee concluded that there were no equalities issues that could be addressed in the guidance.

Conclusion

Esketamine is not recommended

3.35 The committee took into account the unmet need for effective treatment options and the innovative nature of esketamine. But, based on the committee's most plausible assumptions, the costs and benefits of esketamine were very uncertain. It also noted that the potential position in the treatment pathway would be later than described by the marketing authorisation (see sections 3.3 and 3.4). The committee also expressed a preference for ICERs at a lower range of what NICE normally considers to be cost-effective because of the uncertainty in the appraisal and the likely effect on the NHS. The ICERs for the comparison of esketamine with oral antidepressant and placebo with oral antidepressant were much higher than what NICE considers a cost-effective use of NHS resources. Therefore, esketamine is not recommended, within its marketing authorisation, for use in the NHS 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
August 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 with psychiatric expertise from committee B and committee C also took part in both appraisal meetings.

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 and Adam Brooke
Technical leads

Lucy Beggs and Christian Griffiths
Technical advisers

Gemma Barnacle and Gavin Kenny
Project managers

ISBN: [to be added at publication]