Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2258

esketamine 28mg nasal spray, solution (Spravato®)

Janssen-Cilag Ltd

7 August 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

esketamine (Spravato®) is accepted for use within NHSScotland.

Indication under review: In combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI), for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.

In a phase III study in adults (aged 18 to 64 years) with treatment resistant depression, esketamine plus newly initiated antidepressant significantly reduced the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to week 4 compared with placebo plus newly initiated antidepressant. A significantly lower rate of relapse in patients who received esketamine plus antidepressant over placebo plus antidepressant was demonstrated in a further phase III study.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

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Indication

Esketamine, 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 two different treatments with antidepressants in the current moderate to severe depressive episode.[1]

Dosing Information

The decision to prescribe esketamine should be determined by a psychiatrist. Esketamine is intended to be self-administered by the patient under the direct supervision of a healthcare professional.

A treatment session consists of nasal administration of esketamine and a post-administration observation period. Both administration and post-administration observation of esketamine should be carried out in an appropriate clinical setting.

The dose recommendations for esketamine are shown in Table 1 and Table 2 (adults ≥65 years). It is recommended to maintain the dose the patient receives at the end of the induction phase in the maintenance phase. Dose adjustments should be made based on efficacy and tolerability to the previous dose. During the maintenance phase, esketamine dosing should be individualised to the lowest frequency to maintain remission/response. After depressive symptoms improve, treatment is recommended for at least 6 months.
Each device is single-use, providing 28mg of esketamine in two sprays (one spray per nostril).

Table 1: Recommended dosing for esketamine in adults <65 years.[1]

Induction phase		**Maintenance phase**
Weeks 1-4 :		**Weeks 5-8** :
Starting day 1 dose: Subsequent doses:	56mg 56mg or 84mg twice a week	56mg or 84mg once weekly **From week 9:** 56mg or 84mg every 2 weeks or once weekly
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.		The need for continued treatment should be re-examined periodically.

Table 2: Recommended dosing for esketamine in adults ≥ 65 years.[1]

Induction phase		**Maintenance phase**
Weeks 1-4 :		**Weeks 5-8** :
Starting day 1 dose: Subsequent doses:	28mg 28mg, 56mg or 84mg twice a week, all dose changes should be in 28mg increments	28mg, 56mg or 84mg once weekly, all dose changes should be in 28mg increments **From week 9:**

		28mg, 56mg or 84mg every 2 weeks or once weekly, all dose changes should be in 28mg increments
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.		The need for continued treatment should be re-examined periodically.

Blood pressure should be assessed prior to administration of esketamine and should be reassessed approximately 40 minutes after and subsequently as clinically warranted. Because of the possibility of sedation, dissociation and elevated blood pressure, patients must be monitored by a healthcare professional until the patient is considered clinically stable and ready to leave the healthcare setting. Patients with clinically significant or unstable cardiovascular or respiratory conditions require additional precautions.

See Summary of Product Characteristics (SPC) for further details.[1]

Product availability date

18 December 2019

Summary of evidence on comparative efficacy

Esketamine is the S-enantiomer of racemic ketamine. It is a non-selective, non-competitive, antagonist of the N-methyl-D-aspartate (NMDA) receptor.[1]

TRANSFORM-2 and TRANSFORM-3 were multicentre, randomised, double-blind phase III studies which evaluated the efficacy and safety of esketamine plus newly initiated oral antidepressant compared with placebo plus newly initiated oral antidepressant in adult patients with treatment-resistant depression (TRD). Eligible patients were aged 18 to 64 years in TRANSFORM-2 and ≥65 years in TRANSFORM-3, had moderate to severe depression (Inventory for Depressive Symptomatology-Clinician (IDS-C) score ≥34 [≥31 for TRANSFORM-3]), and the episode of depression was either a single episode lasting ≥2 years or recurrent (as per Diagnostic and Statistical Manual of Mental Disorders [DSM]-5 criteria). TRD was defined as nonresponse to an adequate trial (dosage, duration, and adherence) of at least two antidepressants in the current episode, of which one was observed prospectively in the 4-week screening phase. Non response in the screening phase was defined as ≤25% improvement in Montgomery-Asberg Depression Rating Scale (MADRS) score from week 1 to week 4 and a MADRS score ≥28 (≥24 for TRANSFORM-3) at weeks 2 and 4.[2, 3]

Patients who had not responded to the prospective antidepressant treatment by the end of the screening phase entered the 4-week double-blind treatment phase, at which time they discontinued all current antidepressant treatments and were randomised equally to receive esketamine (TRANSFORM-2: n=114; TRANSFORM-3: n=72) or placebo (TRANSFORM-2: n=109;

TRANSFORM-3: n= 66) both in combination with a newly initiated antidepressant. In TRANSFORM-2, esketamine was administered intranasally at a dose of 56mg on day 1. On days 4, 8, 11, and 15 the dose could be increased to 84mg or maintained at 56mg based on the investigator's clinical judgement of efficacy and tolerability. After day 15 the dose remained stable, and continued to be administered twice weekly. In TRANSFORM-3 (elderly patients), esketamine was administered intranasally at a dose of 28mg on day 1. On day 4, the dose could be 28mg or 56mg. On days 8, 11, and 15 the dose could be 28mg, 56mg or 84mg based on the investigator's clinical judgement of efficacy and tolerability. Dose increases were not permitted after day 15, however dose decreases were permitted throughout the treatment period. Twice weekly dosing was maintained throughout the 4 weeks. Investigators, using clinical judgment and prior history, selected one of four new open-label oral antidepressants (duloxetine, escitalopram, sertraline, or venlafaxine extended release) which were administered daily. Randomisation was stratified according to country and class of oral antidepressant (SSRI or SNRI).[2, 3]

The primary efficacy outcome of both studies was change in MADRS score from baseline (day 1) to day 28. MADRS is a clinician-administered questionnaire where total scores range from 0 to 60, with higher scores indicating more severe depressive symptoms. Efficacy analyses were performed in all randomised patients who received at least one dose of intranasal study medication and one dose of oral antidepressant medication. TRANSFORM-2 met its primary outcome; patients treated with esketamine plus oral antidepressant experienced statistically significant improvements in depressive symptoms. In TRANSFORM-3, numerical improvements in depressive symptoms were reported in the esketamine plus oral antidepressant group compared with placebo however these failed to achieve statistical significance. See Table 3.[2-4]

Table 3. Primary outcome results of TRANSFORM-2 and TRANSFORM-3:Mean change in MADRS total score from baseline to day 28 [1, 4]

Study	Treatment group	Mean baseline score	LS mean change from baseline to end of week 4	LS mean difference versus placebo (95% CI)
TRANSFORM-2 (18-64 years)	Esketamine plus OAD (n= 114)	37.0	-17.7	-3.5 (-6.7 to -0.3)*
	Placebo plus OAD (n= 109)	37.3	-14.3	
TRANSFORM-3 (≥65 years)	Esketamine plus OAD (n= 72)	35.5	-10.1	-2.9 (-6.5 to 0.6)**
	Placebo plus OAD (n= 65)	34.8	-6.8	

CI = confidence interval; LS = least squares; OAD = oral antidepressant; * = statistically significant result; ** = median unbiased estimate (that is weighted combination of the LS means of the difference from OAD plus placebo), and 95% flexible CI.

TRANSFORM-2 had the following key secondary outcomes: proportion of participants with onset of clinical response (defined as a ≥50% reduction in MADRS score) by day 2 maintained to the end of the double-blind treatment phase with one excursion (that is, a ≥25% reduction relative to baseline MADRS was allowed on day 8, 15, or 22); change from baseline to week 4 in Sheehan Disability Scale (SDS) scores; and change from baseline to week 4 in 9-item Patient Health Questionnaire (PHQ-9) scores. The SDS is a widely used patient reported outcome that measures disruption to occupational, social and family function, factors which are not adequately captured in the MADRS. The PHQ-9 is another patient reported outcome which evaluates depressive symptom domains of the nine DSM-5 MDD criteria; this was used to complement the clinician-reported MADRS.[4]

The primary and three key secondary outcomes were controlled for type I error through the use of sequential testing, where a result was only considered significant if the previous outcome in the sequence was significant at the two sided 0.05 level. The first key secondary outcome in TRANSFORM-2 did not achieve statistical significance and consequently the other two key secondary outcomes could not be tested formally. In TRANSFORM-3, secondary outcomes were not formally tested but were generally supportive of esketamine plus antidepressant over placebo plus antidepressant. See Tables 4 and 5.[2]

Table 4. Key secondary outcomes TRANSFORM-2 [2]

Key secondary outcome	Esketamine plus OAD (n=114)	Placebo plus OAD (n=109)
Clinical response on day 2[A]	7.9%	4.6%
- Odds ratio (95% CI)	1.79 (0.57 to 5.67) p= 0.321	
Mean change from baseline to week 4 in SDS score*	-13.6	-9.4
Mean change from baseline to week 4 in PHQ-9 score*	-13.0	-10.2

A = clinical response defined as a ≥50% reduction in MADRS score by day 2 maintained to the end of the 4-week double-blind treatment phase with one excursion—that is, a ≥25% reduction relative to baseline MADRS was allowed on day 8, 15, or 22; * = these outcomes could not be formally tested due to the failed statistical hierarchy; OAD = oral antidepressant; CI = confidence interval; LS = least squares; SDS = Sheehan Disability Scale; PHQ-9 = 9-item Patient Health Questionnaire.

Table 5. Secondary outcomes TRANSFORM-3 (FAS population).[3]

Secondary outcomes	Esketamine plus OAD (n= 72)	Placebo plus OAD (n= 65)
Rate of response at week 4 (LOCF)[A]	24%	12%
Rate of remission at week 4 (LOCF)[B]	16%	6.3%
Median change from baseline to week 4 in CGI-S	-1.0	0
Mean change from baseline to week 4 in PHQ-9	-6.0	-3.3
Mean change from baseline to week 4 in SDS	-6.1	-3.8

A = response defined as ≥50% improvement in MADRS score from baseline; B = remission defined as MADRS score ≤12; OAD = oral antidepressant; LOCF = last observation carried forward; CGI-S = Clinical Global Impression− Severity; PHQ-9 = 9-item Patient Health Questionnaire; SDS = Sheehan Disability Scale.

TRANSFORM-1 was a 4-week, randomised, double-blind, active-controlled, phase III study that recruited adult patients (aged 18–64 years) with recurrent or single-episode TRD (non-response to ≥1 but ≤5 OADs in the current episode of depression). Patients (n=346) were randomised equally to a newly initiated antidepressant plus intranasal esketamine 56mg (fixed dose) twice weekly for 4 weeks (n=117), intranasal esketamine 84mg (fixed dose [initial dose of 56mg]) twice weekly for 4 weeks (n=116), or intranasal placebo for 4 weeks (n=113). Randomisation was stratified by country and by class of oral antidepressant (SSRI or SNRI).[5]

The primary outcome was the change in MADRS total score from baseline to day 28. Efficacy analyses were performed in all randomised patients who received at least one dose of esketamine or placebo and oral antidepressant. Esketamine at both doses was numerically favoured over placebo but the results were not statistically significant: least squares mean difference (95% CI) between esketamine 84mg and placebo= -3.2 (-6.88 to 0.45), 2-sided p-value= 0.088; least squares mean difference (95% CI) esketamine 56mg and placebo = -4.1 (-7.67 to -0.49, 2-sided p-value not formally tested.[5]

SUSTAIN-1 was a randomised, double-blind, phase III study which evaluated the efficacy and safety of esketamine plus antidepressant compared with placebo plus antidepressant in patients with TRD in stable remission (defined as MADRS score ≤12 for ≥3 of the last 4 weeks, with one excursion [MADRS score >12] or one missing MADRS assessment permitted at week 13 or 14 only) or response (defined as ≥50% reduction from baseline in MADRS score) after an induction and optimisation course of esketamine plus an oral antidepressant. Patients could enter the study by transferring from the TRANSFORM studies (1 or 2) or by direct entry. The eligibility criteria for SUSTAIN-1 were identical to TRANSFORM-2 (described above).[6]

Patients in stable remission or stable response were separately randomised (1:1) to continue esketamine treatment or discontinue esketamine and switch to placebo nasal spray, whilst continuing to take oral antidepressant treatment. The dose of antidepressant was to remain unchanged throughout the maintenance phase. Randomisation was stratified according to country.[6]

The primary outcome was cumulative distribution of time to relapse during the maintenance phase among patients who achieved stable remission. Relapse was defined as a MADRS total score of ≥22 for two consecutive assessments separated by 5 to 15 days, or hospitalisation for worsening depression, suicide attempt or suicide prevention, completed suicide, or another clinically relevant event suggestive of relapse (assessed by a relapse adjudication committee). The primary outcome was assessed in the primary analysis set, defined as all patients that had achieved stable remission after 16 weeks of esketamine plus antidepressant treatment.[6]

Significantly fewer relapse events occurred during the maintenance phase in the esketamine plus antidepressant group compared with the placebo plus antidepressant group. See Table 6 for further details.[6]

Table 6. Primary outcome - SUSTAIN-1 Time to relapse. Primary analysis set (patients with stable remission at baseline of maintenance phase).[4, 6]

	Esketamine plus OAD (n=90)	Placebo plus OAD (n=86)
Number of relapses[A] (%)	24 (27%)	39 (45%)
Median time to relapse (days)	NE	273
Hazard Ratio (95% CI), p value	0.49 (0.29 to 0.84), p=0.03	
KM estimate of relapse at 12 weeks	13%	37%
KM estimate of relapse at 24 weeks	32%	46%

Abbreviations: CI = confidence interval; NE = not estimable; KM = Kaplan-Meier; OAD = oral antidepressant
A = Relapse was defined as a MADRS total score of ≥22 for 2 consecutive assessments separated by 5 to 15 days, or hospitalisation for worsening depression, suicide attempt, suicide prevention or completed suicide, or another clinically relevant event suggestive of relapse (assessed by a relapse adjudication committee).

In patients who achieved stable response at baseline of the maintenance phase (secondary analysis), continued treatment with esketamine plus antidepressant delayed relapse compared with placebo plus antidepressant. See Table 7 for more details.[6]

Table 7. Key secondary outcome - SUSTAIN-1: Time to relapse in patients who achieved stable response at baseline of maintenance phase.[6]

	Esketamine plus OAD (n=62)	Placebo plus OAD (n=59)
Number of relapses[A] (%)	16 (26%)	34 (58%)
Median time to relapse (days)	635	88
Hazard Ratio (95% CI)	0.30 (0.16-0.55)	

Abbreviations: CI = confidence interval; NE = not estimable; KM = Kaplan-Meier; OAD = oral antidepressant
A = Relapse was defined as a MADRS total score of ≥22 for 2 consecutive assessments separated by 5 to 15 days, or hospitalisation for worsening depression, suicide attempt, suicide prevention or completed suicide, or another clinically relevant event suggestive of relapse (assessed by a relapse adjudication committee).

Other secondary outcomes analysed at the end of the maintenance phase included clinician-rated severity of depressive illness (MADRS and CGI-S), patient-reported depressive symptoms (PHQ-9), anxiety symptoms (GAD-7), functioning and associated disability (SDS), and health-related quality of life and health status (EQ-5D-5L). These were analysed in both remitters (primary analysis set) and responders, and were generally supportive of the benefit of esketamine plus antidepressant over placebo plus antidepressant.[6]

SUSTAIN-2 was a non-comparative, long-term (1-year), open-label, multicentre, phase III safety study that also reported efficacy data for esketamine plus antidepressant. Eligible patients were adults (aged ≥18 years) with recurrent or single-episode TRD (non-response to ≥2 OADs in the current episode of depression). Patients were all taking esketamine, flexibly dosed at 28mg, 56mg, or 84mg, plus an oral antidepressant. A total of 802 patients were enrolled in this study. Of the 779 patients who entered the induction phase (including 88 non-responders from TRANSFORM-3), most patients (74%; 580/779) continued to the optimisation/maintenance phase. Of the 802 patients, 364 (45%) were treated for 6 months and 136 (17%) for 12 months. Efficacy outcomes included change over time in: MADRS, PHQ-9, CGI-S, GAD-7, EQ-5D-5L, and SDS, and response and

remission rates over time based on MADRS and PHQ-9. Overall, treatment with esketamine plus antidepressant resulted in improvements during the 4-week induction phase in measures of depressive symptoms, their severity, and associated disability (MADRS, PHQ-9, SDS, CGI-S, GAD-7, and EQ-5D-5L), which were maintained over the duration of the 48-week optimisation/maintenance phase.[4]

Summary of evidence on comparative safety

Safety data was collected from 1,708 patients across several short and longer-term studies. The safety profile was consistent across all studies. Pooled safety data from TRANSFORM-1/2 and data from SUSTAIN-1 are described below.[4]

In TRANSFORM-1/2 (treatment phase), any treatment-emergent adverse event (TEAE) was reported by 87% of patients in the esketamine plus antidepressant groups (n= 346) and 64% in the placebo plus antidepressant group (n= 222). Most TEAEs were reported post-dose on the day of dosing and resolved the same day. A large number of TEAEs (psychiatric, gastro-intestinal or cardiovascular disorders) are in accordance with established adverse drug reactions for esketamine, or can be derived from its anaesthetic potential. Most TEAEs were mild to moderate, only a minority were assessed as severe. Dose effects were described only for the TEAE of dissociation.[4]

The most frequently reported AEs of any grade with an incidence >15% in the esketamine groups (n= 346) versus the placebo groups (n= 222) were: nausea (28% versus 8.6%), dissociation (27% versus 3.6%), vertigo (22% versus 2.3%), dizziness (24% versus 6.8%), headache (20% versus 17%), dysgeusia (19% versus 14%) and somnolence (17% versus 9.0%).[4]

In SUSTAIN-1 (maintenance phase), any treatment-related adverse event (AE) was reported by 82% of patients in the esketamine plus antidepressant group (n= 152) and 46% in the placebo plus antidepressant group (n= 145). In the esketamine and placebo groups respectively, AE possibly related to nasal spray drug were reported in 82% versus 26% of patients and AE possibly related to oral antidepressant were reported in 8.6% versus 6.2% of patients. One or more serious AE were reported by 2.6% versus 0.7% of patients. AE leading to withdrawal of nasal spray drug were reported in 2.6% versus 2.1% of patients, and AE leading to oral antidepressant being withdrawn were reported in 2.0% versus 0% of patients.[8]

The most frequently reported AEs of any grade with an incidence >15% in the esketamine group (n= 152) versus the placebo group (n= 145) in the maintenance phase were: dysgeusia (27% versus 6.9%), vertigo (25% versus 5.5%), dissociation (23% versus 0%), somnolence (21% versus 2.1%), dizziness (20% versus 4.8%), headache (18% versus 9.7%), nausea (16% versus 0.7%), and blurred vision (16% versus 0.7%).[6]

Overall, the EMA considered that esketamine when given with a SSRI/SNRI had an acceptable tolerability and that the risks were manageable provided that administration was under the supervision of a healthcare professional.[4]

Summary of clinical effectiveness issues

Major Depressive Disorder (MDD) is a common relapsing/remitting psychiatric disorder. In Scotland, it is estimated that MDD affects 11% of the population at any one time. Approximately one third of patients with MDD will not achieve remission after the first or second course of treatment using currently approved medicines, highlighting a need for the development of new therapies. TRD, defined as MDD that has not responded to treatment with at least two oral antidepressants in the current depressive episode, is particularly debilitating and potentially life-threatening due to suicide. At present there are no medicinal products specifically licensed for TRD. The most common treatments are oral antidepressants, which can be given as monotherapy, combination therapy (two antidepressants), or augmentation therapy (antidepressant plus antipsychotic or lithium). Psychological interventions such as cognitive behavioural therapy (CBT) or electroconvulsive therapy (ECT) can be used either in conjunction with pharmacological treatment or as standalone treatment. The choice of intervention should be influenced by the duration of the episode of depression and the trajectory of symptoms, previous course of depression and response to treatment, likelihood of adherence to treatment and any potential adverse effects, and a person's treatment preference and priorities.[4, 9-11]

Several studies have been conducted to investigate the efficacy of esketamine in TRD, including short-term studies (TRANSFORM-1, 2, and 3) and longer-term studies (SUSTAIN-1 and 2).

The primary outcome in TRANSFORM-2 and 3, change in MADRS score, is an appropriate primary outcome to demonstrate short-term efficacy and in accordance with the current treatment and development guidelines, literature and clinical practice.[4, 12] A decrease in MADRS score of -2.0 is widely regarded as a clinically meaningful improvement in depressive symptoms.[4] Therefore, the decrease of -3.5 (BOCF analysis) in MADRS score in TRANSFORM-2 between the esketamine plus antidepressant and placebo plus antidepressant groups can be considered both statistically significant and clinically meaningful. In TRANSFORM-3, although statistical significance was not achieved, the estimated treatment difference of -2.9 clearly favours esketamine plus antidepressant and suggests a clinically meaningful benefit over placebo plus antidepressant in elderly patients with TRD. The consistent results between the short-term studies is reassuring. TRANSFORM-1 used a fixed dose design and therefore does not align with the approved licensed posology. The results of SUSTAIN-1 suggest that the treatment effect is maintained in the longer-term; the reduction in relapse events during the maintenance phase in patients with remission at baseline, 27% versus 45% in the esketamine plus antidepressant and placebo plus antidepressant groups respectively, was statistically significant.[4, 6]

The potential for unblinding in TRANSFORM-2, 3, and SUSTAIN-1 was high and difficult to mitigate due to the dissociative and sedative adverse effects of esketamine. The EMA concluded that the

dissociative effects of esketamine leading to unblinding likely had an effect on effect size, however not to a significant extent.[2-4, 6]

The generalisability of the study findings may be limited by the exclusion of patients with significant psychiatric or medical comorbidities, substance or alcohol dependence, prior nonresponse to ECT in the current episode, and imminent risk of suicide, defined as patients who had suicidal ideation with intent in the previous 6 months or suicidal behaviour in the previous 12 months.[2] Patients meeting these exclusion criteria could represent a sizeable proportion of the population that are eligible under the licensed indication. TRANSFORM-3 enrolled elderly patients (aged ≥65 years), however numbers of patients in the ≥75 years subgroup were too small for any conclusions to be made.[4]

Although an active comparator was used in all of the relevant studies, the comparator groups may not be fully reflective of Scottish clinical practice. Patients in Scotland receiving oral antidepressant for TRD are unlikely to receive the same amount of therapeutic contact (eight clinic visits in four weeks) as they did in TRANSFORM-2 and 3. It has previously been suggested in the literature that an increase in healthcare professional interaction has a positive impact on therapeutic treatment effect in the field of depression. However, it is not clear the nature of the patient-healthcare professional interaction that occurred in these studies, or in fact the magnitude of benefit (if any) the patients gained from this increased interaction.

There remains a lack of direct evidence of the efficacy of esketamine compared with relevant comparators such as antidepressants other than SSRI/SNRIs, combination therapy, augmentation therapy, ECT, or psychological therapies (either in conjunction with pharmacological therapy or as standalone treatment). The submitting company presented a Bayesian network meta-analysis (NMA) to assess the relative efficacy of esketamine plus antidepressant versus relevant comparators in Scottish practice in adult patients with TRD. However, the level of heterogeneity in this NMA was high and the results were unreliable.[13, 14]

Clinical experts consulted by SMC considered that the introduction of this medicine is likely to impact on the patient and service for several reasons. From the patient perspective, administrations have to be supervised by a healthcare professional, for a minimum of 40 minutes because of the possibility of sedation, dissociation and elevated blood pressure. Administrations can be as frequent as twice weekly, but may reduce in frequency with longer-term use. Patients are also unable to drive or operate machinery for the rest of the day following esketamine administration, which may be a burden for patients and/or carers. Increased clinic time and staffing levels are likely to be required to ensure the safe administration and monitoring of esketamine, which is a controlled drug with recognised abuse potential. Clinical experts consulted by SMC considered that esketamine in practice may be reserved for more severe or treatment resistant depression than the licensed indication.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis evaluating esketamine in combination with an SSRI or SNRI within its licensed indication for the treatment of adults with treatment-resistant major depressive disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode. The submitting company presented a comparison with oral anti-depressants alone, weighted for the combination of OADs administered within the control arm of the TRANSFORM-2 study. Clinical expert responses received by the SMC suggest that the esketamine regimen may be used in place of, or following, augmentation therapy with an SSRI or SNRI. Some experts also suggest that electro-convulsive therapy may be an appropriate comparator.

A cohort-based state-transition Markov model was used to estimate the costs and consequences of a course of esketamine treatment. The model utilised four health states relating to depression status ('MDE' [Major Depressive Episode]; 'Response' [MADRS score reduction of 50% or greater, insufficient for remission]; 'Remission' [symptom free or minimal symptoms with MADRS ≤12] and 'recovery' [9 months in remission]), with transitions to remission/response/recovery dependent on the time phase within the model (initiation: 4 weeks; continuation: weeks 5 – 40; maintenance: week 40 onwards). The depression health states were replicated for initial TRD treatment, three lines of subsequent treatment, and an additional three states for best supportive care ('no response', 'response' and 'remission'). Patients could transition to an absorbing health state of death at any time. A 5 year time horizon, 4-week cycle length and a perspective for costs of NHS and social services was used.

Transition probabilities within the model differentiated between the time phase in the model. Transition to the 'response' and 'remission' states at the end of the first cycle utilised response and remission rates from TRANSFORM-2, estimated using a mixed-effects model with repeated measures (MMRM) using observed data. A post-hoc adjustment of these rates was conducted for the comparator cohort only, on the assumption of a constant and proportional effect of additional clinic visits being observed in TRANSFORM-2 that would not translate to clinical practice.[13] Of note, this assumption extrapolated suggested benefits of two additional visits to eight additional clinic visits. From cycle 2 onwards, transitions were mainly defined based on data from the SUSTAIN-1 study (response to remission, response, remission and recovery to subsequent MDE and non-efficacy related treatment discontinuation), with published literature informing subsequent treatments.[15, 16] General population mortality was applied, with an additional mortality risk applied for patients in the MDE and response health states.

Utility estimates were derived using EQ-5D-5L from a pooled analysis of the TRANSFORM-2 study, and preference weights applied for a UK population using the algorithm by van Hout et al 2012, as appropriate.[17] Mean utilities for response (0.764) and remission (0.866) were derived from patients who had completed 28 days of treatment, while for the MDE state a baseline value was used (0.417). Patients in recovery were assumed to have consistent utility to those in remission. Adverse event disutilities were not considered in the base case, although was considered in a scenario analysis. Caregiver disutility was included in the initial base case, however a revised base case excluding carer impacts was obtained to align with SMC methods and is the focus of the results shown below.

Medicine acquisition and treatment administration costs were included in the analysis, alongside healthcare resource use associated with each of the health states. Dose and dose frequency were consistent with the TRANSFORM-2 clinical study, and assumed that two nurses (one band 4 and one band 5) would be required to prepare and administer treatment, with a band 5 nurse monitoring patients following esketamine treatment for 1.25 hours. It was assumed that 6 patients could be treated and monitored by 2 nurses simultaneously. In the base case, 35% of patients were assumed to discontinue esketamine after nine months, with all patients assumed to discontinue by two years. The mean 28-day costs for each health state (MDE: £980.08; response: £164.46; remission: £164.46; recovery: £83.75) were estimated from a comprehensive chart review conducted by the submitting company which included English and some Scottish patients. Additional costs of introducing a new service for esketamine were not included in the analysis.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

The base case results are shown in Table 8, with key scenario analyses in Table 9. The incremental QALYs were driven predominantly by the increased proportion of esketamine patients entering the 'recovery' phase, while a higher proportion of comparator patients remained in the MDE health state. Costs of esketamine treatment represent the highest incremental cost, while costs of management in the MDE health state represent the greatest saving.

Table 8: Base case results with PAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
OAD	£48,802	2.218			
ESK-NS + OAD	£49,169	2.570	£367	0.352	1,042
Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant ICER, incremental cost-effectiveness ratio; LYG, life years gained; OAD oral antidepressant; QALYs, quality-adjusted life years.					

Table 9: Key scenario analyses with PAS

		Base case	Scenario	ICER (£/QALY)
	Base case			1,042
1.	Post-hoc remission and response rate adjustment for OAD	Remission (18.0%) and response (34.0%) rates adjusted for 6 additional clinic visits	Unadjusted remission (31.0%) and response (52.0%) rates	6,979
2.	Time horizon	5 years	2 years	14,821
3.			7 years	-649 (ESK-NS Dominant)
4.	Inclusion of adverse events	Excluded	Costs and disutility included	1,148
5.	MDE utilities	Baseline values (pre-treatment)	Day 28 values (consistent with 'response' and 'remission')	1,509
6.	Caregiver disutility	Excluded*	Disutility of 0.122 applied to MDE state	826
7.	Alternative OAD 4-week relapse and loss-of-response risk in maintenance phase	Data obtained from SUSTAIN-1 (relapse: 12.3%, lost response: 14.9%)	Maintenance phase data from STAR*D study (relapse: 9.24%, lost response: 22.4%)	2,257
8.	Alternative esketamine discontinuation rates	35% of patients discontinue at 9 months; 99.9% at 2 years	0% at 9 months; 94.45% at 2 years	3,607
9.			No discontinuation except loss of efficacy	25,139
10.	Increased esketamine administration costs per session	2 nurses to 6 patients (£30.08)	2 nurses to 1 patient (£180.48)	10,956
11.	Pooled data for TRANSFORM-2 and TRANSFORM-3	TRANSFORM-2 data only (patients aged 18 – 64 years)	TRANSFORM-3 (patients aged ≥65 years)	1,312
12.	Alternative transition probabilities for subsequent treatment	Response and remission from STAR*D adjusted	Observed 12-week response and remission	4,037

		downwards	rates applied in first cycle[+]	
13.	MDE health state costs	£980	Lower cost of MDE health state using lower 95% CI (£761.48)	7,135
14.	Combined scenario	As base case	Combination of: 1, 4, 5, 7, 8 *plus* Lower CI of MDE costs (£761.48/28days) Use of last-observation carried forward efficacy data, exclusion of a mortality effect of TRD.	33,983

There are a number of limitations to the analysis which have the potential to introduce bias. Those that are likely to have the biggest impact on the results are as follows:

- Comparisons were provided against a weighted OAD comparator, as well as scenarios for a number of individual treatment strategies. However, clinical expert input received by the SMC suggests that cognitive behavioural therapy and potentially ECT may be alternative approaches. Costs of CBT and ECT are reflected in the health state costs, but the influence on treatment effectiveness is not. This may reduce the generalisability of the submitted evidence to Scottish clinical practice.
- The post-hoc adjustment of the placebo arm introduces bias in favour of esketamine. While evidence suggests additional appointments may be beneficial for TRD, several weaknesses exist with the assumptions of this approach. In particular, that the data from Posternak et al can generalise to administration visits within the TRANSFORM-2 study, that increasing the frequency of visits continues to result in a linear improvement beyond the observed data, and that the benefits of additional clinic visits continue to be conferred over the longer-term. Given these limitations, use of the unadjusted (pre-specified) response and remission rates from TRANSFORM-2 is likely more appropriate and result in an increased ICER (Scenario 1).
- A number of assumptions have been made in the modelling of subsequent treatment lines, which are likely to result in a significant underestimation of the probability of response and remission to subsequent treatments. The effect of this is to result in far more patients remaining in the MDE health state within the time horizon. This approach may introduce bias in favour of esketamine, and a scenario has been obtained highlighting upward sensitivity to unadjusted data from STAR*D (Scenario 12).
- No costs have been included relating to the initial and ongoing costs of introducing a new service pathway for delivery of esketamine. Clinical expert feedback received by the SMC suggests the costs of introducing a new service will be substantial. As such, the assumptions used in the model are likely to underestimate the cost to the NHS for introducing esketamine into the treatment pathway.

- Linked to the above, an assumption is made that six patients can be supervised simultaneously by two nurses at any one time. While this may be feasible for some clinics, it also apparently assumes that a service is available solely for delivery of esketamine. This contradicts the submitting company's position that esketamine delivery can be incorporated into existing healthcare services. It also may reduce the generalisability of the assumption that additional clinic visits will result in improved response/remission rates. A conservative scenario assuming a higher cost of administration results in an increased ICER (Scenario 10). Discussions at SMC suggested that this may represent a conservative assumption in term of staffing ratios, but was useful in providing a proxy for the sensitivity of the ICER to the inclusion of any relevant service set up costs.
- The majority of longer-term transition probabilities are derived from the SUSTAIN-1 study, where all patients received 16 weeks of esketamine prior to randomisation. This creates a generalisability concern, as patients within the NHS will not previously have received esketamine in standard practice. An alternative scenario utilizing the STAR*D study for OAD response rates may be more appropriate, although represents a naïve comparison (Scenario 7).
- Assumptions relating to the discontinuation of esketamine have not been adequately explored, and may underestimate both the total costs of treatment as well as overestimating post-discontinuation effectiveness. A conservative scenario assuming treatment continues until loss of response highlights considerable sensitivity to this assumption (Scenario 9). SMC clinical experts have suggested that there may be ongoing treatment beyond 2 years in a proportion of patients. Scenarios 8 and 14 reflect ICERs where around 5% of patients continued on therapy.
- An inconsistent approach to the derivation of health state utilities has been applied for the MDE health state, where a baseline value is used, versus the response and remission states, where 'on-treatment' utilities are applied. This may underestimate the 'on-treatment' utility in the MDE health state, and lead to exaggerated QALY gains. An alternative scenario using day 28 values from TRANSFORM is likely more appropriate (Scenario 5).
- The applicability of the source of MDE costs is currently unclear. Although it aligns with the licensed indication, an apparent disparity is created as the trial populations providing effectiveness estimates applied more strict eligibility criteria which may exclude some of the characteristics associated with higher resource use requirements. Corresponding health state costs from similar previous submissions to the SMC have been significantly lower than estimated by the submitting company. The model is highly sensitive to changes in the cost of managing MDE; use of estimates from the lower confidence interval were applied in scenario 13 and the conservative combined scenario (Scenario 14).
- Due to the combined number of approaches which may introduce bias, the ICER could plausibly increase beyond the levels modelled by the submitting company in the base case (as indicated by Scenario 14). Some further combined scenarios were provided following the New Drugs Committee meeting with ICERs in the range £16-25k with PAS.

Despite the uncertainties described above, the economic case was considered demonstrated.

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published "Depression in adults: recognition and management. Clinical guideline [CG90]" in October 2009. CG90 recommends for people with moderate or severe depression a combination of antidepressant medication and a high-intensity psychological intervention such as CBT or IPT. The choice of intervention should be influenced by the duration of the episode of depression and the trajectory of symptoms, previous course of depression and response to treatment, likelihood of adherence to treatment and any potential adverse effects, and a person's treatment preference and priorities. When an antidepressant is to be prescribed, it should normally be an SSRI in a generic form because SSRIs are equally effective as other antidepressants and have a favourable risk–benefit ratio. Combinations of medications should normally be initiated in consultation with a consultant psychiatrist. If a person with depression is informed about, and prepared to tolerate, the increased side-effect burden, consider combining or augmenting an antidepressant with lithium, an antipsychotic such as aripiprazole, olanzapine, quetiapine or risperidone, or another antidepressant such as mirtazapine or mianserin. ECT can be considered for acute treatment of severe depression that is life-threatening and when a rapid response is required, or when other treatments have failed.[9]

In 2015, the British Association for Psychopharmacology (BAP) published a revised guideline called "Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines". In patients with treatment resistance, the guideline suggests there are three options supported by varying quality of evidence: dose increases (supportive evidence is limited), switching antidepressant (either another medicine from the same class or a different class), or augmentation/combination treatment (where adding quetiapine, aripiprazole or lithium are considered first-line, and risperidone, olanzapine, tri-iodothyronine or mirtazapine as second-line). CBT and other psychological treatments should also be considered in conjunction with pharmacological therapy.[18]

Additional information: comparators

Antidepressants, either as monotherapy, combination therapy, or augmentation therapy. Psychological therapies such as CBT and ECT.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Esketamine	**Weeks 1 to 4** Starting day 1 dose = 56mg Subsequent doses = 56mg or 84mg twice a week **Weeks 5 to 8** 56mg or 84mg once weekly **From week 9** 56mg or 84mg every 2 weeks or once weekly	**£11,084 to £27,221**
Esketamine (≥65 years old)	**Weeks 1 to 4** Starting day 1 dose = 28mg Subsequent doses = 28mg, 56mg, or 84mg twice a week (all dose changes should be in 28mg increments) **Weeks 5 to 8** 28mg, 56mg, or 84mg once weekly (all dose changes should be in 28mg increments) **From week 9** 28mg, 56mg, or 84mg every 2 weeks or once weekly (all dose changes should be in 28mg increments)	**£5,542 to £26,895**

After depressive symptoms improve, treatment is recommended for at least 6 months.[1] Costs from MIMS online on 03 March 2020. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated that there would be 4,448 patients eligible for treatment with esketamine in year 1 and 4,497 patients in year 5 and that 165 patients would be treated with esketamine in year 1 rising to 582 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 17 July 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the

considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.