Cost-effectiveness of esketamine (Spravato®), in combination with a SSRI or SNRI, for the treatment of treatment-resistant major depressive disorder in adults.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of esketamine (Spravato®). Following assessment of the applicant's submission, the NCPE recommends that esketamine (Spravato®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Janssen Sciences Ireland UC) economic dossier on the cost effectiveness of esketamine (Spravato®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

National Centre for Pharmacoeconomics **March 2021**

Summary

In August 2020, Janssen Sciences Ireland UC submitted a dossier examining the cost-effectiveness of esketamine, in combination with a selective serotonin re-uptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI), for treatment-resistant major depressive disorder (TRD), in adults who have not responded to at least two different antidepressant treatments in the current moderate to severe depressive episode. Esketamine was granted a marketing authorisation by the EMA for this indication on the 18 December 2019. Esketamine is a N-methyl D-aspartate (NMDA) receptor antagonist and is available as an intranasal spray. Esketamine is administered at a dose of 28mg, 56mg or 84 mg at flexible dosing intervals, depending on response and the phase of treatment. In the acute phase of treatment, esketamine is given twice weekly, with dosing frequency extending to weekly or fortnightly in the maintenance phase. Final data was received from the Applicant on 27 August 2020.

Reimbursement for esketamine is being assessed as a hospital only drug. However, based on clinical opinion obtained by the Review Group, eligible patients with TRD who are treated in community psychiatric clinics may be prescribed esketamine.

Commonly used treatment strategies in clinical practice include combination antidepressant therapy and augmentation therapy (where agents such as lithium and atypical antipsychotics are used with oral antidepressant monotherapy or combination antidepressant therapy). Oral antidepressant monotherapy with older agents such as tricyclic antidepressants and monoamine oxidase inhibitors may be used less frequently. Electroconvulsive therapy has restricted availability within Irish clinical practice and is usually reserved as a last resort or when a rapid response is required. Therefore, combination and augmentation therapies are considered the main comparators.

1. **Comparative effectiveness of esketamine (Spravato®)**

Clinical evidence for the efficacy of esketamine was based on three short-term, phase three studies (TRANSFORM-1 (n=346), TRANSFORM-2 (n=227) and TRANSFORM-3 (n=138)), one longer-term, phase three, randomised withdrawal study (SUSTAIN-1; direct-entry patients

n=437; transferred-entry patients n=286) and one long-term safety study (SUSTAIN-2; direct-entry patients n=691; transferred-entry patients n=111). In the TRANSFORM studies, the efficacy of newly initiated esketamine and newly initiated oral antidepressant therapy (SSRI or SNRI) was compared to that of placebo nasal spray and newly initiated oral antidepressant therapy (SSRI or SNRI) over a four-week period. SSRI or SNRI monotherapy consisted of either escitalopram, sertraline, duloxetine or venlafaxine. The primary efficacy endpoint was mean change from baseline to study endpoint (day 28) in Montgomery-Åsberg Depression Rating Scale (MADRS) score. In TRANSFORM-2, where a flexible dosing regimen of esketamine was permitted, esketamine and oral antidepressant monotherapy demonstrated superior efficacy to placebo and oral antidepressant monotherapy (least squares mean difference -4.0 (95% CI -7.31 to -0.64; two-sided p=0.020). However, no statistically significant difference was detected between treatment arms in TRANSFORM-1, and TRANSFORM-3. The former used a fixed dosed regimen for esketamine in adults aged less than 65 with the latter focussing on the efficacy of flexibly dosed esketamine in a population with TRD aged 65 years and over.

In SUSTAIN-1, participants who were stable remitters[1] (n=175) or stable responders[2] (n=121) on esketamine and oral antidepressant monotherapy after 16 weeks of treatment were re-randomised to either esketamine and oral antidepressant monotherapy or placebo and oral antidepressant monotherapy in the maintenance phase. The time to relapse was significantly delayed in participants who remained on esketamine compared with those in the placebo arm (weighted HR 0.49, 95% CI 0.29 to 0.84; two-sided p=0.003). Almost half (48%) of the relapses in the placebo arm occurred within the first four weeks of re-randomisation. EQ-5D data were collected in all phase three studies.

The Review Group noted a number of limitations with the direct clinical evidence including, but not limited to; the absence of consistency in efficacy across all three acute phase studies; use of a MADRS threshold of 12 instead of a MADRS threshold ≤10, usually used to define remission in clinical studies; a lack of generalisability to Irish clinical practice; potential unblinding bias in participants re-randomised to placebo in SUSTAIN-1 and the lack of direct comparative evidence with relevant comparators such as combination and augmentation treatments.

[1] Stable remission was defined as a MADRS total score ≤12 for at least three of the last four weeks of the optimization phase, with one excursion of a MADRS total score >12 or one missing MADRS assessment permitted at optimization Week 13 or 14 only.

[2] Stable response was defined as ≥50% reduction in the MADRS total score from baseline in each of the last 2 weeks of the optimization phase, but without meeting criteria for stable remission.

The Applicant conducted a network meta-analysis (NMA) to provide indirect evidence of the comparative efficacy of esketamine relative to combination and augmentation treatment strategies. However, the Applicant and the Review Group do not consider the NMA to provide reliable estimates of comparative efficacy. Therefore, in both the Applicant and the NCPE adjusted base cases, only relative efficacy estimates from randomised controlled trials involving oral antidepressant monotherapy (SSRI or SNRI) were considered.

2. Safety of esketamine (Spravato®)

The primary safety assessment was based on patients who received at least one dose of esketamine in six completed phase two and three trials (n=1,708). The mean duration of exposure to esketamine across the phase three trials (n=1,601) was 137.2 days (SD 126.20 days) whereas the mean duration of exposure to placebo and oral antidepressant monotherapy (n=432) was 90.1 days (SD 117.31).

Esketamine is considered to have a safety profile consistent with that of ketamine; esketamine is a S-enantiomer of ketamine. Across TRANSFORM-1, TRANSFORM-2 and SUSTAIN-1, the proportion of patients with treatment-emergent adverse events (TEAEs) possibly related to treatment was higher in the esketamine and oral antidepressant monotherapy group (69.7% to 78.3%) compared with TEAEs in the placebo nasal spray and oral antidepressant monotherapy group (45.5% to 64%). Most TEAEs were mild to moderate, occurring and resolving on the day of dosing. The most common TEAEs (≥10% of participants) with esketamine and oral antidepressant monotherapy across TRANSFORM-1 and TRANSFORM-2 were nausea (28%), dissociation (27%), dizziness (24%), vertigo (23%), headache (20%), dysguesia (19%), somnolence (17%), paresthesia (12%), hypoaesthesia and hypoaesthesia oral (11%). In the corresponding placebo and oral antidepressant monotherapy groups, the TEAEs reported in ≥10% of participants were headache (17%) and dysguesia (14%).

Further long-term data are required to classify the effect esketamine has on cognitive disorders, interstitial cystitis and lower urinary tract symptoms. Due to the possibility of sedation, dissociation and hypertension, patients must be monitored and assessed by a

healthcare professional at each treatment session, encompassing a period of 100 to 120 minutes. While there were no reports of drug-seeking behaviours in the trials, risk minimisation strategies to minimise the potential for drug abuse are outlined in the SPC. Similarly, there are insufficient data to conclude that esketamine did not contribute to three suicides in the esketamine and oral antidepressant monotherapy arms across the studies. Therefore, warnings regarding suicide risk have been included in the SPC.

3. Cost effectiveness of esketamine (Spravato®)

The cost effectiveness of esketamine and oral antidepressant monotherapy was assessed using a Markov model with a cycle length of 28 days and time horizon of five years. The model defined five health states: major depressive episode (MDE), Response, Remission and Recovery, as well as a death state. The model is further described in terms of phases of treatment: acute (weeks one to four), maintenance (weeks five to eight), maintenance (weeks nine to 40) and maintenance (week 41 onwards). Only patients who spend at least nine cycles in the Remission health state can transition to the Recovery state. The comparator in the model was oral antidepressant monotherapy. All patients enter the model in the MDE state. In the Applicant's base case, the proportion of patients who transition to either Response or Remission was derived from rates observed in TRANSFORM-2 for the acute phase and SUSTAIN-1 for the maintenance phases. Loss of response and relapse rates for oral antidepressant monotherapy in the maintenance phase were extrapolated from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. The STAR*D trial is the largest study to date to examine the durability of oral antidepressant monotherapy response in patients with MDD and TRD. In the NCPE adjusted base case, data from TRANSFORM-3 also informed acute phase transitions, assuming 29.4% of the population with TRD are aged 65 years and older. The Applicant reported that there were more clinic visits in the TRANSFORM-2 protocol for the placebo and oral antidepressant monotherapy arm than would be anticipated in clinical practice. Therefore, acute phase efficacy estimates from the placebo and oral antidepressant monotherapy arm were adjusted to reflect an enhanced efficacy for the esketamine and oral antidepressant monotherapy treatment arm. The Review Group did not consider this adjustment appropriate and unadjusted results were used in the NCPE adjusted base case. Health state utility values were sourced from TRANSFORM-2. Utility data from TRANSFORM-1 were made available to the Review Group but were not considered

reflective of the licensing for esketamine. Utility data from SUSTAIN-1 were considered unreliable due to the re-randomised study design. Healthcare resource utilisation was informed by a clinical response survey conducted by the Applicant with six clinicians within the Irish healthcare setting. The Review Group updated some cost inputs using Irish data. Adverse events occurring in greater than 5% of the population were accounted for in the model, applying utility decrements sourced from the literature and assuming the cost of one-hour of psychiatric nursing time per adverse event.

Assumptions around discontinuation of treatment once patients reach the Recovery state are the main driver of the economic model. The Applicant assumes discontinuation of esketamine has no effect on health-related quality of life in the model. The Review Group did not agree with the Applicant's assumption regarding accelerated discontinuation upon entering Recovery. In the NCPE adjusted base case, it is assumed that there is no discontinuation of treatment for reasons other than loss of efficacy once patients enter Recovery.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the NCPE adjusted base case and the Applicant's base case assumptions are shown in Table 1 and Table 2, respectively. The Review Group notes that ICERs presented below are based on the cost-effectiveness of esketamine relative to oral antidepressant monotherapy. The Review Group does not consider oral antidepressant monotherapy involving SSRIs or SNRIs to be the most appropriate comparator for the treatment of TRD in Irish clinical practice.

Table 1 Deterministic results from NCPE adjusted base case cost-effectiveness analysis

Treatment	Incremental Costs	Incremental QALYs	ICER
OAD monotherapy	-	-	-
Esketamine + OAD	€17,073	0.21	€79,743 /QALY

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; OAD = oral anti-depressant;
Note: A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 2 Deterministic results from Applicant's base case cost-effectiveness analysis

Treatment	Incremental Costs	Incremental QALYs	ICER
OAD monotherapy	-	-	-
Esketamine + OAD	€5770	0.31	€18,648 /QALY

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; OAD = oral anti-depressant;
Note: A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

In both the NCPE adjusted base case and the Applicant's base case, the probabilistic ICERs were similar to the deterministic ICERs. In the NCPE adjusted base case, the probability of esketamine and oral antidepressant monotherapy being cost-effective compared with oral antidepressant monotherapy was 0% at both a threshold of €20,000 per QALY and €45,000 per QALY.

In the Applicant's base case, the probability of esketamine and oral antidepressant monotherapy being cost-effective compared with oral antidepressant monotherapy was 44.6% at a threshold of €20,000 per QALY and 100% at a threshold of €45,000 per QALY.

Deterministic one-way sensitivity analyses conducted on the NCPE adjusted base case indicated that the risk of remission in the oral antidepressant monotherapy comparator arm was the most influential parameter. Other influential parameters included the unit cost of esketamine, the number of devices used in the acute and maintenance phases, as well as the number of treatment sessions in the recovery phase.

4. Budget impact of esketamine (Spravato®)

The price to wholesaler of esketamine is €195.18 for a 28mg device (excluding VAT). The Applicant estimates that each patient uses a mean of 2.59 devices per treatment session, for a mean of 31.9 treatment sessions based on SUSTAIN-1 data, resulting in a mean treatment cost estimate of €18,948.01 (including rebates and VAT) per patient. The mean number of treatment sessions is estimated to encompass a treatment period of less than one year (around nine months). However, in the NCPE adjusted base case, the mean number of treatment sessions per patient was estimated to be higher (58.88) and continue for over one year, due to the lower rate of discontinuation compared with the Applicant's assumption. For the purposes of estimating annual budget impact, the Review Group retained the Applicant's annual treatment course cost estimate but acknowledge that this is a likely underestimate. The total annual treatment cost of esketamine and oral antidepressant therapy assuming the mean duration of esketamine is under one year, is estimated to be €19,139.92.

The Applicant estimated the cumulative five-year gross drug budget impact of esketamine to be €11.79 million. The Review Group did not consider the epidemiological estimates used by the Applicant to be appropriate as they underestimated the proportion of patients with moderate to severe depression who would be treated in clinical practice and the proportion

of the population with depression who have TRD. Using the Applicant's market share estimates and the Review Group's preferred epidemiological assumptions, it is estimated that 97 patients will be treated with esketamine and oral antidepressant therapy in year one, rising to 250 patients in year five. The Review Group estimated the cumulative five-year gross drug impact of esketamine and oral antidepressant therapy to be €16.9 million.

The Applicant assumes that esketamine and oral antidepressant therapy will proportionally displace use of oral antidepressant monotherapy, combination antidepressant therapy and augmentation therapy (antidepressant therapy in combination with lithium and atypical antipsychotics). The Review Group projected the cumulative five-year net drug budget impact of esketamine and oral antidepressant monotherapy to be €16.62 million. The cumulative five-year net healthcare budget impact is estimated to be €16.77 million, which accounts for health state costs in addition to the monitoring cost associated with esketamine administration. The Review Group considers budget impact estimates to be underestimates due to a lack of consideration for the potential for patients with TRD to access esketamine treatment within community psychiatric settings. Additionally, using the Applicant's discontinuation assumption underestimates the mean number of esketamine treatment sessions per patient, thus reducing budget impact estimates.

5. Patient submissions

No patient submissions were received in support of this submission.

6. Conclusion

Following the NCPE Review Group assessment of the available evidence, the NCPE recommends that esketamine (Spravato®), in combination with a SSRI or SNRI, not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. *

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.