

## Summary

### WHAT IS TREATMENT-RESISTANT DEPRESSION?

Major depressive disorder is a common condition characterized by symptoms of persistent sadness, feelings of hopelessness, loss of interest in usual activities, decreased energy, difficulty concentrating or sleeping, loss of appetite, and thoughts of hurting oneself. Approximately one in three patients in the US with major depressive disorder do not have an adequate response to standard treatment and are considered “treatment-resistant”.

### TREATMENT OPTIONS

Treatment options for individuals with treatment-resistant depression (TRD) include maximizing the dose of existing antidepressant therapy, adding another antidepressant or non-antidepressant medications, such as antipsychotics, to an existing antidepressant therapy, or switching to a new antidepressant. Electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) are used for the most difficult to treat patients. Esketamine (Spravato™, Janssen) is a new therapeutic agent for adults who have not responded to or tolerated multiple antidepressant therapies. Esketamine is similar to ketamine, which is sometimes administered to treat TRD but has not been approved by the US Food and Drug Administration for this indication.

### SUMMARY OF MEETING

Independent appraisal committee votes that evidence is adequate to demonstrate short-term clinical benefits of esketamine versus placebo, but serious concerns remain about the study criteria used to define treatment-resistant depression and the lack of longer-term data on safety and effectiveness. The list price for esketamine is 25-50% higher than ICER’s value-based price benchmark, and the large eligible patient population creates a potential short-term budget challenge.

### POLICY RECOMMENDATIONS

- Manufacturers and researchers should conduct studies directly comparing esketamine and other treatment options using standardized research protocols and outcomes that reflect what matters most to patients; this would allow real-world, long-term assessment of comparative effectiveness.
- Given the considerable uncertainty that remains regarding the longer-term benefits and risks of esketamine, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure that patients are carefully selected and managed by clinicians with the necessary expertise to ensure appropriate care.
- Payers should develop mechanisms to adequately compensate clinicians for the expenses associated with monitoring and delivering esketamine within the specification of the REMS program.

## Clinical Analyses

**How strong is the evidence that esketamine improves outcomes in patients with treatment-resistant depression?**

### ICER EVIDENCE RATINGS

Evidence provides moderate certainty that the addition of esketamine to a newly initiated antidepressant has comparable or better net health benefit, with a small (but non-zero) chance of net harm, compared to newly initiated antidepressant alone.

There was insufficient evidence to judge the net health benefit of esketamine versus ketamine or other therapies for treatment-resistant depression.

### KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

**How effective is esketamine plus antidepressant compared to placebo plus antidepressant?**



\*Did not reach statistical significance in adults ≥65 years of age, although magnitude of improvement was comparable to what was observed in adults <65 years of age.

### Compared to other therapies

Esketamine has not been directly compared in clinical trials to ketamine or other therapies for treatment-resistant depression. In a trial of ketamine, patients had greater symptom improvement on ketamine plus an antidepressant compared to placebo plus an antidepressant after two weeks of therapy.

## Clinical Analyses (continued)

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### HARMS

The most common adverse events associated with esketamine were nausea, dissociation, and dizziness. Patients also experienced sedation and had clinically important increases in blood pressure. Most adverse events resolved within a day of administration. Ketamine has a similar safety profile and can be a drug of abuse.

There was no evidence of misuse or abuse of esketamine in clinical trials, however, because of its similarity to ketamine, esketamine is required to be used under a safety program that ensures its benefits outweigh the risks.

### SOURCES OF UNCERTAINTY

**Effectiveness in a more severe population:**

Clinical experts consider esketamine to be an option for patients with chronic, severe depression, who have failed multiple other therapies. However only 36-40% of studied patients had failed 3 or more therapies in the current depressive episode.

**Limitation of clinical trial:** It is possible patients could tell they were randomly assigned to receive esketamine because of its dissociative symptoms. Information on maintenance of blinding was not reported.

**Heterogeneity of treatment effect:** There is insufficient evidence to determine which patients may derive the most benefit from esketamine and how patients with co-existing psychiatric conditions, such as anxiety disorder, will respond to the therapy.

**Duration of treatment:** Higher rates of relapse have been observed in patients who discontinued esketamine compared to those who continued to take it.

**Short-term safety:** A total of six deaths occurred during the esketamine development program, all in esketamine-treated patients, although none was considered by the investigators to be esketamine-related. Still clinical experts expressed reservations about this occurrence.

**Long-term safety:** The long-term safety of esketamine as well as its potential for misuse or abuse remain unclear.

**Benefits compared to other treatment options:** More robust data are needed to determine how esketamine compares to other therapies for treatment-resistant depression.

## Economic Analyses

### LONG-TERM COST-EFFECTIVENESS

#### Does esketamine meet established willingness-to-pay thresholds for long-term cost-effectiveness?

At its current price, esketamine plus background antidepressant **exceeds commonly accepted thresholds for cost-effectiveness** of \$50,000-\$150,000 per quality-adjusted life year (QALY) gained or per life-year (LY) gained when compared to background antidepressant:

	Esketamine
Cost per QALY gained	\$198,000
Cost per LY gained	\$2,592,000

### COST-ANALYSIS

#### How does the cost of esketamine compare to ketamine?

Given the similarity of ketamine to esketamine, but the lack of data allowing a comparison of efficacy, a cost-analysis was undertaken to compare one-year costs of treatment with esketamine and intravenous ketamine for the treatment of TRD.

	Excluding lost time from work		Including lost time from work	
	First Year Costs	Annual Costs After First Year	First Year Costs	Annual Costs After First Year
Esketamine	\$36,500	\$30,800	\$39,400	\$33,300
Ketamine	\$3,600	\$2,500	\$5,300	\$3,700

## Economic Analyses (continued)

### VALUE-BASED PRICE BENCHMARKS

**What is a fair price for esketamine based on its value to patients and the health care system?**

	Esketamine
Annual List Price*	\$32,400
Annual Price to Achieve \$100,000/QALY Threshold	\$17,700
Annual Price to Achieve \$150,000/QALY Threshold	\$25,200
Discount from List Price Required to Reach Threshold Prices	25%-52%

\*Annual wholesale acquisition cost (WAC), prior to any discounts or rebates

### POTENTIAL SHORT-TERM BUDGET IMPACT

**How many patients can be treated with esketamine before crossing ICER’s \$819 million budget impact threshold?**

Based on discussions during our public meeting, we are issuing an Access and Affordability Alert to make stakeholders aware that, should uptake ramp up, esketamine use could have important impacts on existing health care budgets. Potentially only 16% of eligible Americans with TRD could be treated with esketamine per year before crossing ICER’s potential budget threshold of \$819 million. Even if priced within ICER’s value-based price benchmark range, only between 20% and 30% of all eligible patients with TRD could be treated with esketamine before exceeding the potential budget impact threshold.

## Summary of Votes

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### CLINICAL EVIDENCE

The panel voted the evidence demonstrated that esketamine, taken with a background antidepressant, is clinically superior to a background antidepressant alone. The panel voted unanimously that the evidence was insufficient to distinguish between esketamine and ketamine, TMS, ECT, or olanzapine.

### LONG-TERM VALUE FOR MONEY

Consistent with ICER's value assessment framework, because the incremental cost ratio for esketamine exceed \$175,000 per QALY, it was deemed "low long-term value for money" without a formal vote by the panel.

### OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

During their deliberation, panel members weighed esketamine's other benefits and contextual considerations. They acknowledged esketamine is intended to care for patients with a condition of high severity and a high lifetime burden of illness, and that esketamine offers a novel mechanism of action compared to other approved treatments for TRD, which may allow successful treatment of many patients for whom other available treatments have failed. They also noted that esketamine may allow for patients to return to work and increase productivity.

Nevertheless, a majority of the panel felt that there is uncertainty about the long-term benefits and risks of esketamine, citing the lack of long-term trial evidence.

## Policy Recommendations

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### For Manufacturers

- Manufacturers should engage with key stakeholders in a transparent process to evaluate fair pricing of esketamine based upon the added clinical benefit to patients.
- Manufacturer-sponsored research should enroll patients who match those patients commonly encountered in clinical practice and who are most likely to benefit from treatment.
- Manufacturers and researchers should conduct studies directly comparing esketamine and other treatment options using standardized research protocols and outcomes that reflect what matters most to patients; this would allow real-world, long-term assessment of comparative effectiveness.

### For Payers

- Given the considerable uncertainty that remains regarding the longer-term benefits and risks of esketamine, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure that patients are carefully selected and managed by clinicians with the necessary expertise to ensure appropriate care.
- Prior authorization criteria should be based on clinical evidence, with input from clinical experts and patient groups. Options for specific elements of coverage criteria within insurance coverage policy are discussed in the full report.
- Payers should develop mechanisms to adequately compensate clinicians for the expenses associated with monitoring and delivering esketamine within the specification of the REMS program.

### For Patient Advocacy Organizations

- Patient organizations should seek commitments from government research funding agencies and manufacturers to increase research, both basic and clinical, for common conditions such as treatment-resistant major depressive disorder.

### For Specialty Societies

- Specialty societies should develop a clear definition of response to therapy for patients with TRD.

### For Regulators

- The patient population which may be considered for treatment with esketamine is very large. However, in the short-term, the REMS program may result in a slow expansion of use among patients with TRD. It is unlikely that the manufacturer will feel it has financial incentives to invest in further studies to define long-term risks and benefits, or to evaluate subpopulations which may have distinctive risks or benefits. Regulators have an important role to play in how new therapeutics enter clinical practice and therefore should require post-approval, long-term comparative outcomes studies for treatments like esketamine that are initially evaluated and approved in short-term randomized trials, but for which long-term therapy would be expected for some patients.

## About ICER

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The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website ([www.icer-review.org](http://www.icer-review.org)).