# RE: Drug Repurposing for Unmet Medical NeedsRequest for Information [FDA-2026-N-4492]

BEFORE THE FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

RESPONSE: Nomination of Racemic Ketamine Hydrochloride (IV) for Label Indications in Major Depressive Disorder, Bipolar Depression, and Acute Suicidal Ideation

JOINT STATEMENT ON BEHALF OF: The American Society of Ketamine Physicians, Psychotherapists & Practitioners (ASKP3) and BrainFutures

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## I. EXECUTIVE SUMMARY

This submission nominates intravenous (IV) racemic ketamine hydrochloride for FDA label consideration in three critical unmet medical needs: (1) major depressive disorder (MDD) in adults, including treatment-resistant and severe depressive episodes; (2) depressive episodes associated with bipolar I and bipolar II disorder in adults (bipolar depression); and (3) acute suicidal ideation or suicidal symptoms occurring in the context of MDD or bipolar depression. Racemic ketamine is an off-patent, widely available generic drug currently FDA-approved only as an anesthetic agent.

A robust evidence base, including over 30 randomized controlled trials, multiple Cochrane reviews and meta-analyses, and major clinical practice guidelines, supports its rapid-acting antidepressant effects and clinically meaningful reductions in suicidal ideation at subanesthetic doses, commonly 0.5 mg/kg to 1.0 mg/kg IV over 40 minutes. Formal label approval would improve patient access, standardize clinical practice, support

measurement-based safety monitoring, enable insurance coverage, and address a profound health equity gap relative to the far more expensive FDA-approved intranasal esketamine (Spravato).

International regulatory and guideline bodies have already acted on this evidence. In March 2026, the French drug regulatory agency (Agence nationale de sécurité du médicament et des produits de santé, ANSM) granted the first-ever regulatory approval of IV racemic ketamine for the treatment of adults with severe suicidal symptoms.[1][2] Norway has published a national clinical guideline for IV ketamine in treatment-resistant depression.[3] The UK National Health Service uses IV ketamine to treat severe depression as an alternative to electroconvulsive therapy.[4] These international precedents underscore the maturity of the evidence base and the urgency of U.S. regulatory action.

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## II. IDENTIFICATION OF THE DRUG AND PROPOSED INDICATIONS

**Drug:** Ketamine hydrochloride for injection, USP (racemic mixture of R- and S-enantiomers)

**Current FDA-Approved Indication:** General anesthesia (sole agent or induction agent)

**Proposed New Indications:**

1. Major depressive disorder (MDD) in adults, including severe and treatment-resistant presentations.

> The existing evidence base is strongest for treatment-resistant depression (TRD), defined as inadequate response to at least two adequate antidepressant trials. FDA could reasonably narrow an initial MDD indication to this population. Alternatively, FDA could specify the additional evidence threshold required to support a broader MDD indication, including the necessary trial population, comparator, endpoints, durability data, and safety monitoring requirements.

2. Depressive episodes associated with bipolar I or bipolar II disorder in adults.

> The existing evidence base has focused on individuals co-treated with mood stabilizers. FDA could reasonably narrow this indication to require adjunctive use with mood-stabilizing therapies. Any bipolar depression indication should specify that patients receive appropriate mood-stabilizing treatment and should include monitoring for treatment-emergent hypomania, mania, mixed symptoms, psychosis, and substance misuse.

3. Acute suicidal ideation or suicidal symptoms in adults occurring in the context of MDD or bipolar depression.

> FDA should evaluate whether the existing evidence supports an indication for rapid reduction of suicidal ideation or suicidal symptoms, with or without the presence of comorbid MDD or bipolar disorder. FDA could also clarify what additional evidence would be required to support such labeling, including the appropriate endpoint, time horizon, required concomitant care, durability of effect, and distinction between reduction in suicidal ideation versus prevention of suicide attempts or suicide mortality.

**Proposed Dosing:** 0.5 mg/kg administered intravenously over 40 minutes as the standard starting dose, with response-guided dose escalation up to 1.0 mg/kg for patients with inadequate clinical response, in a medically supervised setting with post-infusion monitoring. This flexible dosing model is supported by a placebo-controlled dose-ranging RCT demonstrating significant efficacy at both 0.5 mg/kg and 1.0 mg/kg, and mirrors the established titration framework used for intranasal esketamine (56 mg to 84 mg).[5] The ASKP3 consensus guidelines further endorse this approach.[6]

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## III. UNMET MEDICAL NEED

### A. Major Depressive Disorder and Treatment-Resistant Depression

Major depressive disorder affects approximately 21 million adults in the United States annually, with an estimated 8.9 million receiving pharmacotherapy. Approximately 2.8 million (31%) of these patients meet criteria for TRD. TRD accounts for a disproportionate share of the disease burden: 56.6% of healthcare costs and 47.7% of unemployment costs attributable to medication-treated MDD, totaling $43.8 billion annually.[7]

Current FDA-approved options for TRD are limited. Intranasal esketamine (Spravato) is approved for TRD and for depressive symptoms in adults with MDD with acute suicidal ideation or behavior, but its high cost (approximately $590 to $885 per treatment session), REMS requirements, and limited insurance coverage create substantial barriers to access.[8] The VA/DoD 2022 Clinical Practice Guideline now recommends ketamine or esketamine for patients who have failed multiple adequate pharmacologic trials, yet the absence of an FDA-approved indication for racemic ketamine limits insurance reimbursement, standardization of care, and equitable access.[9]

### B. Bipolar Depression

Bipolar disorder affects 1% to 2% of the global population, and patients spend the majority of their illness course in depressive episodes. Approximately 25% of patients with bipolar depression experience treatment resistance.[10] Few pharmacotherapies are FDA-approved for bipolar depression (quetiapine, lurasidone, cariprazine, olanzapine-fluoxetine combination, lumateperone), and none provides the rapid onset of action needed for acute suicidal crises. No ketamine-based product is currently approved for bipolar depression. The International Society for Bipolar Disorders (ISBD) Task Force has identified ketamine as a promising novel agent for treatment-resistant bipolar depression (TRBD), noting its rapid antidepressant and anti-suicidal effects.[10]

### C. Acute Suicidality

Suicide is a leading cause of death in the United States, claiming approximately 49,000 lives annually, with 12.2 million adults reporting serious suicidal thoughts and 1.4 million attempting suicide each year, at a combined economic cost of $510 billion annually.[11-15] Emergency department visits for suicide attempts and intentional self-harm nearly quadrupled from 1.43 million in 2011–2012 to 5.37 million in 2019–2020, yet fewer than 16% included evaluation by a mental health professional.[16] A critical treatment gap exists: conventional antidepressants require weeks to reduce suicidal ideation, and no pharmacotherapy is currently FDA-approved with a primary indication for the rapid reduction of suicidal ideation or prevention of suicidal behavior.[16][17] The only FDA-approved ketamine-based product for MDD with acute suicidal ideation (intranasal esketamine) is approved for the treatment of

depressive symptoms in this population, but not for suicidal ideation itself, and its high cost and limited insurance coverage create the same access barriers described above.[18]

The absence of any FDA-approved rapid-acting anti-suicidal pharmacotherapy represents a significant unmet need in psychiatric medicine, particularly given the rising burden of suicidal crises presenting to emergency departments nationwide. Formal label approval of IV racemic ketamine for this indication would fill a therapeutic void that no currently approved medication addresses.

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IV. SUMMARY OF SUPPORTING EVIDENCE

A. Efficacy in Treatment-Resistant MDD

The evidence for IV racemic ketamine in TRD has been designated Level 1 evidence (multiple RCTs and meta-analyses) by the Canadian Network for Mood and Anxiety Treatments (CANMAT).[19]

Key findings include:

- Meta-analysis of 26 RCTs (n = 1,166; Shim et al., JAMA Psychiatry, 2026): A single IV ketamine infusion produced significant reductions in depressive symptoms at 4 hours (SMD −1.74), 24 hours (SMD −1.15), 3 days (SMD −0.97), and 1 week (SMD −0.89). Repeated infusions showed sustained benefit (SMD −0.81 at end of treatment).[1]

- Meta-analysis of 36 RCTs (n = 2,903; Bahji et al., Expert Opinion on Drug Safety, 2022): Treatment with ketamine was associated with improved response (RR 2.14; 95% CI 1.72–2.66), remission (RR 1.64; 95% CI 1.33–2.02), and depression severity (d = −0.63) vs. placebo, with no significant increase in dropouts or adverse events.[20]

- Cochrane Systematic Review (Dean et al., 2021; 64 studies, 5,299 participants): Ketamine increased response and remission compared with placebo at 24 hours (OR 3.94; 95% CI 1.54–10.10).[21]

- Dose-ranging RCT (Fava et al., 2020; n = 99): Both 0.5 mg/kg and 1.0 mg/kg IV ketamine were significantly superior to active placebo (midazolam) on the primary outcome (HAM-D-6), while lower doses (0.1, 0.2 mg/kg) were not significant after adjustment for multiple comparisons. The 1.0 mg/kg dose was well tolerated with greater dissociative symptoms but no serious adverse events.[5]

- Dose-frequency RCT (Singh et al., Am J Psychiatry, 2016; n = 68): Twice-weekly IV ketamine (0.5 mg/kg) for 2 weeks produced a 69% response rate and 37.5% remission rate vs. 15% and 7.7% with placebo in the twice-weekly dosing arm.[22]

- Network meta-analysis (Terao et al., 2024): IV racemic ketamine was significantly more effective and acceptable than intranasal esketamine and aripiprazole as augmentative treatments for TRD.[23]

B. Efficacy in Bipolar Depression

- Systematic review (Bahji et al.; Int J Neuropsychopharmacol, 2021): Overall response rate of 61% with IV ketamine vs. 5% with placebo. All studies used 0.5 mg/kg IV racemic ketamine as add-on to mood stabilizers.[24]

- Cochrane Systematic Review (Dean et al., 2021; 10 RCTs, 647 participants): A single IV ketamine dose was more effective than placebo for response at 24 hours (OR 11.61; 95% CI 1.25–107.74) and depression score reduction (mean difference −11.81).[25]

- Retrospective study (Cuomo et al., n = 59; J Affect Disord, 2025): IV ketamine in treatment-resistant bipolar depression produced significant MADRS score reductions with no manic switches and was well tolerated despite polypharmacy.[26]

- Real-world effectiveness data (Fancy et al., Bipolar Disorders, 2023): Repeated IV ketamine infusions demonstrated sustained effectiveness in treatment-resistant bipolar depression in a real-world clinical setting.[27]

- ISBD Task Force (Vieta et al., 2025): Identified ketamine as showing rapid antidepressant and anti-suicidal effects in TRBD, with a 51% response rate after a single infusion.[10]

C. Anti-Suicidal Efficacy

- The Shim et al. 2026 JAMA Psychiatry meta-analysis demonstrated significant reductions in suicidal symptoms at 24 hours (SMD −0.69) and 1 month (SMD −0.70) after a single infusion, and at end of treatment after repeated infusions (SMD −0.72).[1]

- The VA/DoD Clinical Practice Guideline for Assessment and Management of Patients at Risk for Suicide (2024) supports ketamine infusions as adjunctive treatment for short-term reduction of suicidal ideation in patients with MDD.[44]

- The ISBD Task Force noted that ketamine's anti-suicidal effects may occur independently of its overall antidepressant effect, which is particularly relevant in TRBD given the high suicide risk in this population.[10]

D. Comparative Effectiveness vs. Esketamine

Multiple studies suggest IV racemic ketamine may be at least as effective as, and potentially superior to, intranasal esketamine:

- A network meta-analysis found IV racemic ketamine significantly more effective and acceptable than intranasal esketamine for TRD.[23]

- An observational study (Singh et al., n = 62) found faster time to remission with IV ketamine vs. intranasal esketamine (HR 5.0, p = 0.02).[28]

- A retrospective chart review (Meisner et al., n = 153) found IV ketamine produced a 49.2% reduction in QIDS-SR16 scores vs. 39.6% with intranasal esketamine over an induction period, with significance reached after 1 treatment for IV ketamine vs. 2 treatments for esketamine.[29]

- A cost-effectiveness analysis found IV ketamine dominated intranasal esketamine from a healthcare sector perspective, yielding more QALYs at lower cost.[8]

- A large-scale, PCORI-funded Phase 3 RCT is underway: the EQUIVALENCE trial (Non-inferiority, Comparative Effectiveness Study of Intravenous Ketamine vs. Intranasal Esketamine for Treatment-Resistant Depression; ClinicalTrials.gov Identifier: NCT06713616).[30]

E. Dose-Response Evidence and Rationale for Flexible Dosing (0.5 to 1.0 mg/kg)

The proposed dose range of 0.5 to 1.0 mg/kg is supported by converging evidence from randomized controlled trials, meta-analyses, naturalistic studies, and real-world clinical protocols:

- Dose-ranging RCT (Fava et al., 2020): The only multi-site, placebo-controlled trial to directly compare subanesthetic ketamine doses. Ninety-nine patients were randomized across five arms (0.1, 0.2, 0.5, 1.0 mg/kg, and midazolam placebo). Both 0.5 mg/kg and 1.0 mg/kg were significantly superior to placebo on the primary outcome (HAM-D-6), while lower doses were not after adjustment for multiple comparisons. The 1.0 mg/kg dose was well tolerated, with greater dissociative symptoms and transient blood pressure elevations but no serious adverse events.[5]

- Meta-analysis of dose-response (Nikolin et al., EClinicalMedicine, 2023; 29 RCTs, 2,665 participants): Higher doses of racemic ketamine produced the largest reductions in depression severity both after a single session (SMD = −0.73) and during repeated administrations (SMD = −0.61). The authors concluded that adequate dosage, ideally response-guided on an individual basis, should be recommended in clinical settings to optimize efficacy outcomes.[31]

- Naturalistic inpatient study (Vestring et al., 2024; n = 77, 1,068 administrations): In patients with multiple treatment-resistant depression, high-dose IV ketamine (0.75 to 1.0 mg/kg) resulted in the most pronounced clinical effects, with no adverse events requiring medical intervention.[32]

- Real-world clinical protocol (Canadian Rapid Treatment Center of Excellence): The CRTCE protocol starts patients at 0.5 mg/kg and escalates to 0.75 mg/kg for the 3rd and 4th infusions if inadequate response (≤20% reduction in QIDS-SR16) is observed, demonstrating the clinical feasibility and safety of response-guided dose escalation.[33]

- JAMA Psychiatry Consensus Statement (Sanacora et al., 2017): Acknowledges that the use of alternative doses and routes of administration could be appropriate for individual patients under specific conditions, including dose adjustment for high BMI, and recommends that alternative dosing be disclosed during informed consent.[41]

- Meta-analysis of dose escalation (Seshadri et al., 2024): While this analysis concluded that higher IV ketamine doses (>0.5 mg/kg) did not lead to statistically greater treatment response at the meta-analytic level, the authors noted the small number of included studies and low overall quality of evidence. Importantly, no additional safety signals were identified at higher doses, and the analysis does not demonstrate that 1.0 mg/kg is less effective than 0.5 mg/kg.[34]

The proposed response-guided titration strategy (starting at 0.5 mg/kg with escalation up to 1.0 mg/kg for non-responders) mirrors the flexible dosing model already established for intranasal esketamine (56 mg to 84 mg). This approach maximizes the likelihood of clinical response while maintaining the well-established safety profile of subanesthetic ketamine.

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V. SAFETY PROFILE

A. Acute Safety

Across 26 RCTs in the Shim et al. 2026 meta-analysis, reported serious adverse events (hospitalizations, deaths) were unrelated to ketamine. Other adverse events (dissociation, headache, nausea, transient blood pressure elevation) were mild, transient, and resolved during the observation period.[1] A comprehensive review of adverse effects confirmed that the majority are mild, transient, dose-dependent, and attenuate with subsequent treatments.[35]

In the Fava et al. dose-ranging trial, the 1.0 mg/kg dose produced greater dissociative symptoms and transient blood pressure elevations compared to 0.5 mg/kg, but all effects were self-limited and no serious adverse events occurred at any dose tested (0.1, 0.2, 0.5, or 1.0 mg/kg).[5]

B. Real-World Safety Evidence

Additional real-world evidence of safety demonstrating infrequent serious adverse events in a 40,000-infusion dataset has been submitted to the FDA through a Broad Agency Announcement, currently under FDA review (FY26C3CP16).

C. Abuse Potential and Mitigation

Ketamine is a Schedule III controlled substance. The Sanacora et al. 2017 JAMA Psychiatry consensus statement recommends that all doses be administered under medical supervision, with monitoring for substance use, and that dosing frequency be limited to the minimum necessary to achieve clinical response. The proposed indication would require administration in a medically supervised setting, analogous to the REMS framework for esketamine but leveraging existing clinical infrastructure.

D. Long-Term Safety Considerations

Concerns about cognitive impairment and bladder toxicity derive primarily from chronic high-dose recreational use (>1 g/day), not from clinical subanesthetic dosing.[36] A large clinical trial of intranasal esketamine (doses up to 84 mg, administered weekly or biweekly for an average of 3 years) found maintained or slightly improved cognitive function in adults with MDD.[36] Real-world data on racemic ketamine treatment for up to six months demonstrated sustained effectiveness (response rates of 35% at 8 weeks and 44.2% at 6 months) with good tolerability when structured safety monitoring was employed.[37]

E. Safety in Bipolar Disorder

In a 59-patient study of IV ketamine in treatment-resistant bipolar depression, no manic switches were observed during the treatment period, and adverse events were generally mild to moderate.[26] Across the broader literature, only 2 participants (1 receiving ketamine, 1 receiving placebo) developed manic symptoms.[20]

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VI. REGULATORY PATHWAY CONSIDERATIONS

A. International Regulatory Precedent

In March 2026, the French National Agency for Medicines and Health Products Safety (ANSM) granted the first regulatory approval in history for IV racemic ketamine for the

treatment of adults with severe suicidal symptoms.[2] This landmark decision was based on the same body of RCT evidence summarized in this submission and establishes a critical international precedent for U.S. regulatory action. The UK National Health Service already uses IV ketamine to treat severe depression as an alternative to electroconvulsive therapy, and Norway has published a national clinical guideline for IV ketamine in treatment-resistant depression, further demonstrating international consensus on the clinical readiness of this intervention.[3-4]

B. 505(b)(2) NDA Pathway

Racemic ketamine hydrochloride for injection is an established, well-characterized drug with decades of clinical use and extensive safety data. A 505(b)(2) New Drug Application would allow the sponsor to reference the existing body of published literature and the approved NDA for ketamine as an anesthetic, supplemented by the substantial RCT evidence summarized above.[38] This pathway is specifically designed for situations where a drug's safety profile is well established and new clinical data support a new indication.

C. "Labeling-Only" 505(b)(2) Approach

As proposed by Crittenden et al. (2024), a "labeling-only" 505(b)(2) NDA could enable approval of a new indication for a well-established generic drug without requiring new chemistry, manufacturing, and controls (CMC) data or introducing new drug products into the marketplace. This approach is particularly well-suited to racemic ketamine, where multiple generic products are already available and the clinical evidence base is robust.[40]

D. Barriers to Repurposing and the Role of FDA Action

The primary barrier to formal approval of IV racemic ketamine for depression is economic: no manufacturer has sufficient market incentive to sponsor a new indication for an off-patent generic drug. This is precisely the type of market failure that the FDA's drug repurposing initiative is designed to address. Without FDA action, the current situation will persist: widespread off-label use without standardized labeling, inconsistent insurance coverage, and inequitable access that disproportionately affects patients who cannot afford out-of-pocket costs.

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VII. GUIDELINE, EXPERT CONSENSUS, AND INTERNATIONAL REGULATORY SUPPORT

The following major clinical practice guidelines, expert consensus statements, and international regulatory actions support the use of IV racemic ketamine for depression:

- French Drug Regulatory Agency (ANSM, March 2026): Granted the first regulatory approval in history for IV racemic ketamine for the treatment of adults with severe suicidal symptoms, establishing a landmark international precedent for formal indication approval.[2]

- Norwegian National Clinical Guideline (2026): Published a national clinical guideline for the use of IV ketamine in treatment-resistant depression in Therapeutic Advances in Psychopharmacology, providing a government-endorsed framework for clinical implementation.[3]

- UK National Health Service: IV ketamine is already used within the NHS to treat severe depression as an alternative to electroconvulsive therapy, as noted in the 2026 Lancet depression seminar.[4]

- ASKP3 Consensus Guidelines (2026): The American Society of Ketamine Physicians, Psychotherapists, and Practitioners (ASKP3) published interdisciplinary, Delphi-driven consensus guidelines for the use of IV ketamine infusions for depressive disorders, achieving consensus on 73 of 75 guideline items across seven key practice areas to standardize clinical practice, improve patient outcomes, and promote equitable access.[6]

- CANMAT Task Force (2021): Third-line recommendation for IV racemic ketamine in adults with TRD, with Level 1 evidence for single-dose efficacy.[19]

- VA/DoD Clinical Practice Guideline for MDD (2022): Recommends ketamine or esketamine for patients who have not responded to several adequate pharmacologic trials.[9] The VA Pharmacy Benefits Management Services, National Formulary Committee, and Office of Mental Health have since provided National Protocol Guidance for Ketamine Infusion for Treatment Resistant Depression and Severe Suicidal Ideation. [45]

- JAMA Psychiatry Consensus Statement (Sanacora et al., 2017): Endorsed clinical use of ketamine for mood disorders with specific recommendations for patient selection, monitoring, and administration. The statement also endorses individualized dose adjustment under appropriate conditions, noting that alternative doses could be appropriate for individual patients.[41]

- ISBD Task Force on TRBD (Vieta et al., 2025): Identified ketamine as a promising novel agent for treatment-resistant bipolar depression.[10]

- Mayo Clinic Depression Center Panel (2026): Strong consensus recommending ketamine/esketamine as next-step treatment for TRD.[42]

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VIII. PUBLIC HEALTH IMPACT AND HEALTH EQUITY

Formal FDA approval of IV racemic ketamine for TRD and bipolar depression would:

1. Standardize care: Provide a labeled dosing regimen (0.5 to 1.0 mg/kg with response-guided titration), monitoring requirements, and safety framework to replace the current patchwork of off-label practices, along with requirements for collection of long-term safety data and outcomes.

2. Align FDA standards across enantiomers: To our knowledge, the REMS requirements for esketamine, and the unrestricted use of off-label of racemic ketamine, represents the only instance of such marked regulatory differences between single enantiomers of the same molecule. Re-labeling racemic ketamine allows the FDA to align safety standards across enantiomeric molecules.

3. Expand access and reduce costs: Increase insurance coverage and reduce out-of-pocket costs for millions of patients with MDD/TRD and bipolar depression who currently cannot access or afford intranasal esketamine. IV racemic ketamine costs approximately $5 to $10 per vial vs. $590 to $885 per esketamine treatment session, and has been shown to dominate

esketamine in cost-effectiveness analyses, even when accounting for the similar labor costs for administering the two treatments.[8]

4. Address health equity: The current system, in which the only FDA-approved ketamine-based antidepressant is a high-cost branded product, creates a two-tiered system of access that disproportionately disadvantages uninsured, underinsured, and rural patients.

5. Reduce suicide: Ketamine's rapid anti-suicidal effects are likely to be life-saving in acute settings, and formal approval would facilitate its integration into emergency and inpatient psychiatric care pathways, especially in the context of Spravato's existing indication for adults with MDD who have acute suicidal ideation or behavior.

6. Align with international standards: Multiple countries, including France (regulatory approval), Norway (national clinical guideline), and the United Kingdom (NHS clinical use), have already formally endorsed IV racemic ketamine for depression. U.S. FDA action would bring American regulatory standards into alignment with international practice.

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IX. CONCLUSION

IV racemic ketamine hydrochloride represents one of the most compelling candidates for drug repurposing in medicine. The evidence base includes over 30 RCTs, multiple Cochrane reviews and meta-analyses, Level 1 evidence designation by CANMAT, endorsement by the VA/DoD, ISBD, ASKP3, and other major guideline bodies, and the prior international regulatory approval for these indications. The drug is off-patent, inexpensive, widely available, and has a well-characterized safety profile spanning decades of clinical use, including real-world safety data from over 40,000 infusions currently available for FDA review. Formal FDA approval for MDD/TRD, bipolar depression, or acute suicidality would address critical unmet medical needs, improve health equity, align U.S. practice with international standards, and save lives. We respectfully urge the FDA to prioritize racemic ketamine hydrochloride for its drug repurposing initiative.

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Respectfully submitted,

Sandhya Prashad, MD (President) and Nicolas Grundmann, MD, MBA (Member) on behalf of The American Society of Ketamine Physicians, Psychotherapists & Practitioners (ASKP3).

Sarah Norman (Executive Director) on behalf of BrainFutures

6/9/2026

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