Cognitive and Operational Performance Effects of Intranasal Ketamine
Needs Statement and Military Relevance

Need:
There exists an Army need to determine if the administration of intranasal ketamine in sufficient doses to grant moderate to severe pain relief elicits cognitive impairment, including hallucinations and other psychotomimetic events.

Relevance:
Treatment of combat casualties with morphine leads to inability of the soldier to function effectively.

Intranasal ketamine may be an effective analgesic without adverse cognitive side effects.
Goal

To demonstrate whether ketamine, applied intranasally as self-medication by the individual Warfighter, can manage moderate to severe pain while allowing the Warfighter to remain cognitively functional.

Operational context includes the potential for pain relief and mission continuation, including effective defense and possible mission accomplishment.

Overarching Hypothesis:

Subjects treated with a self-administered intranasal ketamine product remain cognitively functional as determined by successful performance on military-relevant tasks.
Background: Product profile

**PMI-100 (intranasal ketamine hydrochloride 100 mg/mL)**

**Dosing**
- 0.10 mL metered nasal spray (10 mg/spray)
- Titration up to 5 sprays under supervision
- Interval of $\geq$ 90 seconds between sprays
- Dosing every 3 hours as required

**Clinical Profile**
- Onset of action 4 minutes post dose
- Duration of action 2-2.5 hours
- Mean titrated effective dose 43.5 to 46 mg
- Effective dose range 30 to 40 mg
Effective Analgesic Dose:

- Optimal Dose is 3 to 5 sprays (30 – 50 mg)
- Absolute bioavailability PMI-100 = 35.5%

Therapeutic Index

- 15 X difference between analgesic and anesthetic dose

**Analgesic Dose of 50mg PMI-100 (50mg*35.5%) = 18 mg**

**Anesthetic Dose of IV Ketamine (Ketalar® ) = 280 mg**
Intranasal Ketamine (PMI-100)

Intranasal ketamine is primarily absorbed through the nasal mucosa

- Not inhaled – avoids lungs
- Not ingested – avoids GI system
- Avoids first pass metabolism

Relief from moderate to severe pain

- Current U.S. Army Morphine protocol allows 10 mg dosing by the Combat Medic
- 50 mg IN Ketamine is approximately equivalent to 7.5 mg I.V. Morphine*

* IDDS MOR-001 (dental pain) vs. KET – 002(orthopedic injury) & KET-003 (dental pain)
Clinical Trial Summary

Studies Completed to Date:

1. **KET-001**: Phase 2 single dose breakthrough pain, \((N=20)\)
2. **KET-002**: Phase 2 single dose orthopedic injury, \((N=40)\)
3. **KET-003**: Phase 2 single dose postoperative, \((N=40)\)
4. **KET-003B**: Phase 2 single dose postoperative, \((N=40)\)
5. **KET-004**: Phase 2 single dose burn pain, \((N=12)\) (Ongoing)
IN Ketamine vs. IV Morphine Sulphate

7.5 mg IV MS (MOR-001) vs 50 mg PMI-100 (KET-003) vs. 46 mg PMI-100 vs. (KET-002).

![Graph showing VAS Pain Intensity Difference over time for different treatments. The x-axis represents time in minutes from 0 to 60, and the y-axis represents VAS Pain Intensity Difference ranging from 0 to 50. The graph compares 7.5 mg IV MS (MOR-001), 50 mg PMI-100 (KET-003), and IN Ketamine (KET-002).]
**Integrated Summary of Safety**

**PMI-100 Safety Summary**

Overall Patient Population
- 117 Subjects treated with all doses of PMI-100
- Opiate tolerant population (N=20)
- Opiate naïve population (N=97)
- 10 mg (N=28), 30 mg (N=19), 50 mg (N=47)

Adverse Events
- No serious adverse events
- No severe adverse events
- No visual hallucinations
- No interventions with benzodiazepines
FDA Meeting Determination

June 2004 end of phase II

- Dose response, onset of action, duration of action, non effective, minimally effective and maximally effective dose determined

- FDA requested additional data on cognitive effects of PMI-100
Integrated Summary

*PMI-100 Dissociative Adverse Events as reported by dissociative questionnaire presented to patients*

- Few events reported, most transient in nature
- Majority were weak to modest in severity
- No hallucinations reported
- Dizziness was reported as bothersome or very bothersome 11/80 (15%)

**Overall Dissociative Adverse events >10%**

- Dizziness 32/80 (40%)
- Fatigue 30/80 (38%)
- Nausea 12/80 (15%) vs. 15% placebo
- Changes in Vision 11/80 (14%)
- Feeling of Unreality 10/80 (13%)
Ketamine Adverse Event Profile

Side Effects Profile

• Anesthetic Doses
  - 11% patients experience “emergence reaction”

• Analgesic Doses (PMI-100, 50 mg)
  - 1 (0.85%) patient experienced “mild” Auditory Hallucination
  - 1 (0.85%) patient experienced “mild” Kinetic Hallucination
Military Operational Performance and Cognitive Assessment Plan
Programmatics

$8.0M effort (equally co-funded $4M DoD, $4M Industry)

$500K initial set aside for cognitive performance wedge

Linked to Army requirements: TRADOC Pamphlet 525-66, FOC-11-05: b(4)(d), Global Casualty Care Management and Evacuation explicitly requires improved drugs to manage pain

Task Area for Battlefield Pain Control established (March 2002)

Advanced Technology Demonstration Master Plan Drafted: Nasal Ketamine for Injury Pain Relief on the Battlefield (March 2003)

Cognitive and Operational Performance Effects of Intranasal Ketamine Integrated Research Team established (June 2004)
Quad Chart / Schedule

Program:
- Mission Reqts / Feasibility
- Success in Pain Management Models
- Prototype Device
- Fieldable Device
- PK Studies
- Decongestant Interference
- Metabolism
- 1 or 2 Nostril Application
- Clinical Trials
- Burn Procedures
- Acute Orthopedic Trauma
- FDA
- NDA
- COTS Item
- Demonstrate No Cognitive Impairment

Legend:
- Actual Start
- Actual End
- Milestone
- Planned Start
- Planned End
- Planned Milestone

U.S. Army Institute of Surgical Research
KPP and Risk

Key Performance Parameter

Main KPP is the ability to demonstrate the occurrence or lack of occurrence of significant performance impairment in operationally relevant demonstrations

Low Technical Risk

Preliminary clinical trials using the same dose range and mode of administration uniformly show no or only minor effects on cognition or psychological parameters

Multiple psychological, neuropsychological, and cognitive performance assessments instruments are being considered to determine tasks that are sensitive and specific to previously reported effects of ketamine
**Integrated Research Team**

**Mission**

Develop and refine studies that build a sound evaluation strategy on the **militarily relevant performance** effects of intranasal ketamine

Execute an operationally suitable test methodology using a **common set of agreed upon metrics** and affordable design

Produce scientifically-based, reasonable, and realistic recommendations on the **potential use of intranasal ketamine** as an alternative to IV morphine for battlefield pain control

Remain within program cost and schedule requirements as approved in the program baseline
## Multi RAD / Multi Laboratory Effort

<table>
<thead>
<tr>
<th>Agency</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRAIR:</td>
<td>Neuropsych/cognitive task battery selection</td>
</tr>
<tr>
<td></td>
<td>Cognitive dose response studies</td>
</tr>
<tr>
<td>USAISR:</td>
<td>Pain and cognition studies</td>
</tr>
<tr>
<td>USARIEM:</td>
<td>Dismounted soldier performance</td>
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<tr>
<td></td>
<td>Soldier common tasks (i.e., marksmanship)</td>
</tr>
<tr>
<td>USAARL:</td>
<td>Complex (flight*) performance</td>
</tr>
<tr>
<td></td>
<td>Intra-squad / team performance</td>
</tr>
</tbody>
</table>

*Requirement to test mounted (e.g., driver) performance.*
Assessment Tool

- Cambridge Neuropsychological Test Automated Battery (CANTAB)
- Core common battery of 15 tests of cognition that will be correlated with each lab’s specific measures
- Offers a sensitive and specific cognitive assessment tool
- Good test-retest reliability
- Language-independent, non-invasive testing of subjects
- Ease of use and tailoring of tests to our requirements
- Extensively validated with over 250 papers published in peer reviewed journals
- Over 2000 norms for 4-90 year olds, in 4 different IQ bands
- Accurate measure of response along with detailed analyses
- Advanced results handling, with report and spreadsheet generation
**Assessment Tool**

**Big/Little Circle**

Big/Little Circle is a test of the subject's ability to follow an explicit instructional rule, and then to reverse this rule. The subject is presented with a series of pairs of circles, one large and one small. The subject is instructed first to touch the smaller of the two and then after 20 trials to touch the larger.

**Delayed Matching to Sample**

Delayed Matching to Sample presents the subject with a complex visual pattern (the sample) and then, after a brief delay, four patterns between which she or he must choose. Each pattern is made up of four sub-elements, each of a different color. One of the choice patterns is identical to the sample, one is a novel distracter pattern, one has the shape of the sample and the colors of the distracter, and the fourth has the colors of the sample and the shape of the distracter. To discourage strategies based on encoding single quadrants, all four choice patterns have a quadrant in common with the sample.

**ID/ED Shift**

ID/ED Shift is a test of the subject's ability to attend to the specific attributes of compound stimuli, and to shift that attention when required. Two artificial dimensions are used, color-filled shapes and white lines. Two stimuli (one correct, one incorrect) are displayed, initially each of only one dimension, then each of both dimensions (first adjacent, then overlapping as illustrated). Feedback teaches the subject which stimulus is correct, and after six correct responses, the stimuli and/or rules are changed. These shifts are initially intra-dimensional (e.g. color filled shapes remain the only relevant dimension), then later extra-dimensional (white lines become the only relevant dimension).
Assessment Tool

Motor Screening
Motor Screening is a screening task administered before other tests. It introduces the subject to the touch-screen and acts as a training procedure to ensure that the subject can touch the screen accurately. It simultaneously screens for visual and movement problems and ensures that the subject can hear, understand and follow simple instructions. A series of crosses is shown in different locations on the screen. After a demonstration of the correct way to point using the forefinger of the dominant hand, the subjects must touch the crosses in turn.

Paired Associates Learning (PAL)
Paired Associates Learning is a form of delayed response procedure, which tests two different aspects of the ability to form visuo-spatial associations. First, the number of patterns placed correctly on the first presentation of each trial gives an index of 'list memory'. Second, the number of repeat, reminder presentations needed for the subject to learn all the associations provides a measure of 'list learning' (the task can also be conceived as a test of visuo-spatial conditional learning).

Pattern Recognition Memory
Pattern Recognition Memory presents the subject with series of visual patterns in the centre of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, the subjects are required to choose between a pattern they have already seen and a novel pattern. The test patterns are presented in the reverse order to the original order of presentation. This sub-test is repeated with a new set of 12 patterns to be remembered.
Assessment Tool

Matching to Sample Visual Search

Matching to Sample Visual Search is a speed/accuracy trade-off task, testing the subject's ability to match visual samples. An abstract pattern, composed of four colored elements is presented in the middle of the screen. After a brief delay, a varying number of similar patterns is shown in a circle of boxes around the edge of the screen. Only one of these matches the pattern in the centre of the screen and the subject must indicate which it is by touching it. Reaction time is measured on the basis of the release of the press-pad, which allows for its more accurate measurement.

Rapid Visual Information Processing

Rapid Visual Information Processing is a test of vigilance (sustained attention) with a small working memory component. A white box appears in the centre of the computer screen, inside which digits, from 2 to 9, appear in a pseudo-random order, at the rate of 100 digits per minute. Subjects are requested to detect consecutive odd or even sequences of digits (e.g. 2-4-6, 3-5-7, 4-6-8, 5-7-9, etc.) and to register responses using the press-pad. Initially, the computer prompts the subject when sequences appear and gives feedback when the pad is pressed. As the practice part of the test progresses, these cues are gradually phased out, and in the assessment part, no cues or feedback are given.

Reaction Time

Reaction Time has three purposes. First, it trains the subject in holding down the press-pad and touching the screen. Second, it provides a screen for the ability to acquire and perform this motor skill and third, it acts as a simple single and multiple choice reaction time task. Its five stages require increasingly complex chains of responses. In each case, the subject must react as soon as a yellow dot appears. In some stages it may appear in one of five locations, and the subject sometimes responds by using the press-pad, sometimes by touching the screen, and sometimes both.
**Assessment Tool**

**Spatial Recognition Memory**

Spatial Recognition Memory presents the subject with a white square that moves in sequence to five different places on the screen. In the recognition phase the subject sees a series of five pairs of squares, one of which is in a place previously seen in the presentation phase. The other square is in a location not seen in the presentation phase. As with the pattern recognition test, locations are tested in the reverse of the presentation order. This sub-test is repeated three more times, each time with five new locations.

**Spatial Span**

Spatial Span is a test of spatial memory span. White squares are shown, some of which momentarily change in color in a variable sequence. The subject must then touch each of the boxes in the same order as they were originally colored by the computer. The number of boxes in the sequence is increased from 2 at the start of the test 9 by the end. The sequence and color used change from sequence to sequence to minimize interference.

**Spatial Working Memory**

Spatial Working Memory is a test of spatial working memory and strategy performance. The aim of the test is that the subject should find a blue 'token' in each of the boxes displayed and use them to fill up an empty column on the right hand side of the screen, whilst not returning to boxes where a blue token has previously been found. The color and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies.
Stockings of Cambridge

Stockings Of Cambridge is a spatial planning test based upon the 'Tower of London' test. The subject is shown two displays containing three colored balls, presented so they can be perceived as stacks of colored balls in stockings. In each trial, the subject must move the balls in the lower display to copy the pattern shown in the upper. A later motor control task, in which the subject simply copies earlier moves, allows planning time (versus movement time) to be calculated and taken, relative to the number of moves required to complete each trial, as a measure of the subject's planning ability.
IN Ketamine Integrated Research Team

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Backup Slides
Intranasal Ketamine Review

KET-PK-001 Summary

Pharmacokinetics, Dose Proportionality and Absolute Bioavailability of PMI-100 (Intranasal Ketamine) in Healthy Volunteers

2 period, cross-over, IV vs. PMI-100 (10, 30, 50 mg)

- $t_{1/2}$ (h) = 5.8
- $T_{max}$ (h) = 0.42
- Bioavailability 35.3% [90% CI 22.3-55.8]
**KET-001 Summary**

Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of PMI-100 for the Treatment of Breakthrough Pain in Patients with Chronic Malignant Pain

2 period, cross-over, placebo vs. PMI-100 (10 to 50 mg)

- Mean reduction in pain intensity (NPIS) 0 to 60 minutes 2.65 vs. 0.81 (p<0.0001)
- Statistically significant ≥40% reduction in pain intensity (p=0.0078)
- Use of rescue medication 0% vs. 35% (p=0.0156)
- Mean dose 43.5 mg
- Statistically significant reduction in pain intensity at 10 minute timepoint (p=0.0039)
**Intranasal Ketamine Review**

**KET-002 Summary**

Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of PMI-100 for the Treatment of Orthopedic Injury Pain in the Emergency Room

Single dose, parallel group, placebo vs. PMI-100 (10 to 50 mg)

- Mean reduction in pain intensity (VAS) 0 to 60 minutes
  27.2 mm vs. 21.7 mm (p=0.3013)
- Statistically significant \(\geq20\%\) reduction in pain intensity 
  (p=0.0078)
- Use of rescue medication 10\% vs. 35\% (p=0.1274)
- Mean dose 45.8 mg
KET-003 Summary

Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of 10 mg, 30 mg and 50 mg of PMI-100 for the Treatment of Postoperative Dental Pain

Single dose, parallel group, placebo vs. PMI-100 (10, 30 and 50 mg)

- Statistically significant total pain relief over 3 hours (TOTPAR3) for 10, 30 and 50 mg groups
- Statistically significant $\geq 40\%$ reduction in pain intensity VAS ($p=0.0257$)
- Rescue meds in first 3 hours 50% vs. 100% ($p=0.0325$)
- Statistically significant reduction in pain intensity at 10 minute 50 mg PMI-100 timepoint ($p=0.0084$)
- Median time to rescue medication 50 mg PMI-100 [139 minutes] and 30 mg PMI-100 [126 minutes]
Intranasal Ketamine Review

**KET-003B Summary**

Randomized, Placebo-Controlled, Double-Blind, Study of the Safety and Efficacy of 2.5 mg, 5 mg and 10 mg of PMI-100 for the Treatment of Postoperative Dental Pain

Single dose, parallel group, placebo vs. PMI-100 (2.5, 5.0 and 10 mg)

- No statistically significant total pain relief over 3 hours (TOTPAR3) for 2.5, 5.0 and 10 mg groups
## Intranasal Ketamine Adverse Events (>5%)

<table>
<thead>
<tr>
<th>All doses (10-50mg)</th>
<th>50 mg Dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 117</td>
<td>N = 47</td>
<td>N = 61</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Dizziness</td>
<td>Hypertension</td>
</tr>
<tr>
<td>15/117 (12.8%)</td>
<td>12/47 (25.5%)</td>
<td>(4/61) 6.6%</td>
</tr>
<tr>
<td>Peculiar/Bad taste</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>9/117 (7.7 %)</td>
<td>5/47 (10.6%)</td>
<td></td>
</tr>
<tr>
<td>Emesis</td>
<td>Bad taste</td>
<td></td>
</tr>
<tr>
<td>7/117 (6%)</td>
<td>5/47 (10.6%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Difficulty concentrating</td>
<td></td>
</tr>
<tr>
<td>12/117 (10.3%)</td>
<td>3/47 (6.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drowsiness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/47 (6.4%)</td>
<td></td>
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<tr>
<td></td>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/47 (6.4%)</td>
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</tr>
</tbody>
</table>

Source: KET-PK-001, KET-001, KET-002, KET-003, KET-003B
### Comparative Adverse Events in >10% Study Patients

<table>
<thead>
<tr>
<th>IN Ketamine</th>
<th>Fentanyl (Actiq)¹</th>
<th>Morphine (Avinza)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness (12.8 %)</td>
<td>Nausea (23-45%)</td>
<td>Constipation</td>
</tr>
<tr>
<td>Hypertension (10.3 %)</td>
<td>Dizziness (17-16 %)</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Somnolence (15-17%)</td>
<td>Somnolence</td>
</tr>
<tr>
<td></td>
<td>Vomiting (12-31%)</td>
<td>Vomiting</td>
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<tr>
<td></td>
<td>Constipation (4-20%)</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Asthenia (9-38%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache (6-20 %)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anxiety (3-15%)</td>
<td></td>
</tr>
</tbody>
</table>

¹ Physicians’ Desk Reference, 58th edition, 2004
## Comparative Adverse Events in 5-10% Study Patients

<table>
<thead>
<tr>
<th>IN Ketamine</th>
<th>Fentanyl (Actiq)&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Morphine (Avinza)&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peculiar/Bad Taste (7.7%)</td>
<td>Confusion (4-10%)</td>
<td>Peripheral Edema</td>
</tr>
<tr>
<td>Emesis (6.0%)</td>
<td>Insomnia (1-7%)</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Rash (2-8%)</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Accidental Injury (2-9%)</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary tract Infection</td>
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<tr>
<td></td>
<td></td>
<td>Accidental Injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flu Syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Back Pain, Rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sweating, Fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia</td>
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<tr>
<td></td>
<td></td>
<td>Depression</td>
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<tr>
<td></td>
<td></td>
<td>Paresthesia</td>
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<tr>
<td></td>
<td></td>
<td>Asthenia, Dyspnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anorexia, Dry mouth</td>
</tr>
</tbody>
</table>

## Comparative Adverse Events in <5 % of Study Patients

<table>
<thead>
<tr>
<th>IN Ketamine</th>
<th>Fentanyl (Actiq)</th>
<th>Morphine (Avinza)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence (3.4%)</td>
<td>Abnormal Gait (2-4%)</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Headache (3.4%)</td>
<td>Dry Mouth (2-4%)</td>
<td>Withdrawal Syndrome</td>
</tr>
<tr>
<td>Hypoesthesia (2.5%)</td>
<td>Nervousness (2-3%)</td>
<td>Agitation</td>
</tr>
<tr>
<td>Nausea (2.6%)</td>
<td>Vasodilatation (2-3%)</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Tachycardia (2.6%)</td>
<td>Thinking Abnormal (1-2%)</td>
<td>Confusion</td>
</tr>
<tr>
<td>Burning in nose (2.6%)</td>
<td>Sweating (2-4%)</td>
<td>Convulsions</td>
</tr>
<tr>
<td>Euphoric mood, Nasal congestion, Rhinitis, Blurred vision, Feeling abnormal (1.7%)</td>
<td>Abnormal Vision (2-3%)</td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td>Pruritus (2%)</td>
<td>Hallucinations</td>
</tr>
<tr>
<td></td>
<td>Hallucinations (1%)</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>Vertigo (1%)</td>
<td>Vertigo...</td>
</tr>
</tbody>
</table>

Current Status of Ketamine

Ketamine listed as a CSA Schedule III on 8/12/99

TITLE 21 - FOOD AND DRUGS
CHAPTER 13 - DRUG ABUSE PREVENTION AND CONTROL

Definition of Schedule III.

(A) The drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

* Office of Diversion Control, Drug Enforcement Administration, US Department of Justice April 2003
U.S. Army Institute of Surgical Research
Definition of Schedule III Substance

Schedule III and IV substances

“... no controlled substance in schedule III ... may be dispensed without a written or oral prescription ... Such prescriptions may not be filled or refilled more than six months after the date thereof or be refilled more than five times after the date of the prescription unless renewed by the practitioner “

Source: Office of Diversion Control, Drug Enforcement Administration, US Department of Justice April 2003
Dependence

Physical dependence:
changes that have occurred in the body after repeated use of a drug that necessitates the continued administration of the drug to prevent a withdrawal syndrome.

Psychological dependence:
perceived “need” or “craving” for a drug. While physical dependence disappears within days or weeks after drug use stops, psychological dependence can last much longer and is one of the primary reasons for relapse/initiation of drug use after a period of abstinence.  

Addiction Potential of Ketamine

Ketamine is not physically addictive, but there is evidence of tolerance and psychological dependence

- Ketamine does not appear to produce withdrawal symptoms in chronic users. ¹

- Tolerance rises quickly with regular use ¹

- Animal studies support the view that ketamine can give rise to a dependence syndrome without physical withdrawal phenomena²

- Most instances of ketamine self-administration involve sporadic abuse or experimental use or use in a group setting. Only rarely is intensive or compulsive drug use noted³

² Beardsley and Balster, 1987
Risks associated with misuse

Limited mortality associated with ketamine

- 12 deaths in which ketamine was identified between 1987 – 2000. Only three of the fatal cases involved ketamine alone

- Majority of risks associated with bodily-harm due to loss of physical control and lower risk-aversion behavior

- Risk of psychological dependence