

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211243Orig1s000**

**OTHER REVIEW(S)**

---

## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

---

**Date of This Memorandum:** March 5, 2019  
**Requesting Office or Division:** Division of Psychiatry Products (DPP)  
**Application Type and Number:** NDA 211243  
**Product Name and Strength:** Spravato (esketamine) nasal spray, 56 mg dose kit and 84 mg dose kit (28 mg per device)  
**Applicant/Sponsor Name:** Janssen Pharmaceuticals, Inc.  
**FDA Received Date:** March 5, 2019 (via email)  
**OSE RCM #:** 2018-1873-2  
**DMEPA Safety Evaluator:** Loretta Holmes, BSN, PharmD  
**DMEPA Team Leader:** Sevan Kolejian, PharmD, MBA

---

#### 1 PURPOSE OF MEMORANDUM

The Division of Psychiatry Products (DPP) requested that we review the device label, blister labeling, carton labeling and Instructions for Use for Spravato (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review<sup>a</sup> and other Agency recommendations provided to Janssen via email.

#### 2 CONCLUSION

The revised device label, blister labeling, carton labeling and Instructions for Use for Spravato are acceptable from a medication error perspective. We have no further recommendations at this time.

---

<sup>a</sup> Holmes, L. Human Factors Results and Label and Labeling Review for Spravato (NDA 211243). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Feb 28. RCM No.: 2018-1875-1 and 2018-1873-1.

**APPENDIX A. IMAGES OF LABEL AND LABELING (not to scale)**



**Blister Labeling (received on March 5, 2019)**



3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

LORETTA HOLMES  
03/05/2019 04:20:03 PM

SEVAN H KOLEJIAN  
03/05/2019 04:28:28 PM

---

**HUMAN FACTORS RESULTS AND LABELS AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

---

**Date of This Review:** February 28, 2019

**Requesting Office or Division:** Division of Psychiatry Products

**Application Type and Number:** NDA 211243

**Product Type:** Combination Product

**Drug Constituent Name and Strength:** Spravato (esketamine) nasal spray, 56 mg kit and 84 mg kit (28 mg per device)

**Device Constituent:** Nasal Spray

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Janssen Pharmaceuticals, Inc.

**FDA Received Date:** January 30, 2019

**OSE RCM #:** 2018-1875-1 and 2018-1873-1

**DMEPA Safety Evaluator:** Loretta Holmes, BSN, PharmD

**DMEPA Team Leader:** Sevan Kolejian, PharmD, MBA

**DMEPA Associate/Deputy Director:** Irene Z. Chan, PharmD, BCPS

---

## 1 REASON FOR REVIEW

This review is written in response to a request from the Division of Psychiatry Products (DPP) to review Janssen's responses to recommendations we made in our previous human factors (HF) validation study results, label and labeling review<sup>a</sup> and to review the results of the supplemental human factors study report submitted by Janssen on January 30, 2019.

### 1.1 PRODUCT DESCRIPTION

Spravato (esketamine) nasal spray is indicated for treatment-resistant depression (TRD) in adults. The nasal spray device is a single-use device that delivers a total of 28 mg of esketamine in two sprays (one spray per nostril). Spravato is intended for administration by the patient under the supervision of a healthcare provider (HCP), using 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose) with a 5-minute rest between use of each device.

Janssen proposes the following packaging configurations: a carton containing one 28 mg nasal spray device (28 mg dose), a carton containing two 28 mg nasal spray devices (56 mg total dose) and a carton containing three 28 mg nasal spray devices (84 mg total dose). See Appendices A and E.

### 1.2 REGULATORY HISTORY

We previously reviewed the HF validation study protocol<sup>b</sup> for esketamine nasal spray submitted on May 19, 2016 under IND 114345 and the HF validation study results<sup>c</sup> submitted on September 4, 2018. Our review of the HF validation study results concluded the results did not demonstrate the user interface supports the safe and effective use of the product and that Janssen implemented revisions to the user interface without providing additional validation data to demonstrate effectiveness of the revisions. We advised that our recommendations be implemented along with any additional risk mitigation strategies and validated in another HF validation study. Our recommendations were sent to Janssen on January 17, 2019.

One of our concerns during our previous review was that Janssen submitted results from an HF validation study, but that study did not validate the carton labeling that Janssen intended to market and submitted in the original NDA. On January 30, 2019, Janssen submitted responses to our recommendations and submitted the results of a supplemental human factors study that was conducted to assess the revised carton labeling they originally submitted in the NDA. The supplemental study was completed in December 2018. The submission also included revised Instructions for Use (IFU). The IFU revisions were made in response to FDA's recommendations

---

<sup>a</sup> Garrison, N and Holmes, L. Human Factors Labels and Labeling Review for Spravato (NDA 211243). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jan 14. RCM No.: 2018-1875 and 2018-1873.

<sup>b</sup> Holmes, L. Human Factors Protocol Review for Esketamine Nasal Spray IND 114345. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 19. RCM No.: 2016-1230.

<sup>c</sup> Garrison, N and Holmes, L. Human Factors Labels and Labeling Review for Spravato (NDA 211243). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jan 14. RCM No.: 2018-1875 and 2018-1873.

sent on January 17, 2019, but Janssen did not validate the changes they made in the IFU in another HF validation study.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of the material reviewed.

<b>Table 1. Materials Considered for this Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Background Information Previous DMEPA HF Reviews	B
Janssen's responses to recommendations made in our previous human factors (HF) validation study results, label and labeling review	C
Supplemental Human Factors Study Results	D
Product Sample, Labels and Labeling, Packaging	E

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our overall assessment of Janssen's responses to our previous recommendations is described below. Our assessment of the device label, carton labeling, revised blister labeling, and revised instructions for use is also provided.

We note the information provided in the supplemental human factors study results report was incomplete and is insufficient for us to complete an adequate review of the results (e.g., the study protocol, the moderator script, all of the mock prescriptions provided to study participants, and the definitions for performance success, difficulty/close call, and failure were not provided). Therefore, our evaluation of the supplemental human factors study results report is limited given the missing information. Due to the late nature of Janssen's submission, there is inadequate time to obtain and review the additional information needed within the current review cycle. Additionally, we note that the supplemental study conducted by Janssen was limited only to evaluating changes to the carton labeling and not changes to other components of the user interface (e.g., the IFU).

### 3.1 ASSESSMENT OF JANSSEN'S RESPONSES TO RECOMMENDATIONS WE MADE IN OUR PREVIOUS HF VALIDATION STUDY RESULTS LABEL AND LABELING REVIEW

Table 2 provides the recommendations we made in our previous human factors validation study results, label and labeling review; Janssen's responses to our previous recommendations; and our assessment of Janssen's responses.

<b>Table 2: Summary and Analyses of Janssen’s Responses</b>					
<b>Issue #</b>	<b>Identified Issue</b>	<b>Rationale for Concern</b>	<b>FDA Recommendation</b>	<b>Applicant Response</b>	<b>DMEPA Comment</b>
<b>Instruction for Use (IFU)</b>					
1.	The instruction for the patient to blow their nose before first device use only is important information and may be overlooked	Step 1 of the IFU instructs the user to “Get ready” and HCPs are advised before first device only: instruct patient to blow nose before first device only and confirm required number of devices. We note failures in the HF validation study included participant performance and subjective feedback regarding overlooking this step and one HCP recommended relocating the instruction to the section, “Prepare patient” as this was pertaining to the patient.	We recommend that the first image and instruction in Step 3 “Prepare Patient” should be instructing the “...patient to blow nose before first device only.” This may help to minimize the risk for this instruction being overlooked or not carried out.	<p>The Applicant proposes to maintain the current instruction for blowing the nose in Step 1.</p> <p>Moving the blow nose instruction from Step 1 “Get Ready” to Step 3 “Prepare Patient” could result in an underdose due to users blowing their nose between each spray or before each device for 56 mg and 84 mg doses.</p> <p>A previous formative study with the instruction in a similarly proposed location found that many patients were unsure when to blow their nose and indicated that they would blow their nose between sprays or devices.</p> <p>Later revisions to the IFU included the instruction in Step 1 “Get Ready,” to clarify for users that the nose should be blown only once for the first device. This change was assessed in the HF validation study and while it didn’t address all</p>	The Applicant asserts that the residual risk associated with this critical task failure is acceptable. They provided additional new information indicating that formative studies were previously conducted to evaluate this task and the resulting IFU stems from what was learned in formative testing. The formative testing information was not previously evaluated by FDA and details of the results were not submitted by Janssen. To determine the clinical implications of the failure to blow the nose prior to first device use, we sought input from the medical officer. According to the medical officer, the concern is if the nose is clogged, would enough spray actually get inside and be absorbed by the nasal mucosa? This might lead to potential

**Table 2: Summary and Analyses of Janssen’s Responses**

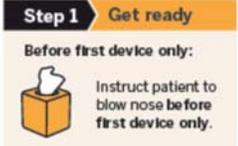
Issue #	Identified Issue	Rationale for Concern	FDA Recommendation	Applicant Response	DMEPA Comment
				<p>use errors, it was assessed as common to all nasal spray devices and acceptable as a residual risk. Below are the relevant instructions in Step 1 and the warning in Step 5 not to blow the nose further. This the right information at the right time of use.</p>  <p>Step 5 instruction:</p>  <b>Do not blow nose.</b>	<p>under dosing. The medical officer stated this is a potential issue, but probably not a major issue as the majority of the users, who aren’t sick or have allergies won’t have a clogged nose and not much in the way even if they don’t blow their nose. We acknowledge that failure of the patient to blow their nose prior to first device use is not a unique requirement for Spravato. There is no data available to help us determine what is substantially below recommended dose for patients who have clogged nose or allergies. We recognize that there is a public health need for Spravato, thus, we will accept the residual risk at this time and will monitor postmarket for any issues that may arise related to this use error.</p>

Table 2: Summary and Analyses of Janssen's Responses					
Issue #	Identified Issue	Rationale for Concern	FDA Recommendation	Applicant Response	DMEPA Comment
2.	The instruction for the HCP to take the device from the patient and check that no green dots are showing is important information and may be overlooked.	Step 5 of the IFU instructs the user to, "Take device from patient. Check that indicator shows no green dots." We note failures in the HF validation study included participant performance and subjective feedback regarding the need to check for the green dots was not fully apparent.	We recommend revising the statement in bold font, " <b>Check that indicator shows no green dots.</b> " to help bring additional prominence to this instruction.	The Applicant agrees to revise the statement in Step 5 of the IFU to bold font: " <b>Check that indicator shows no green dots.</b> "	Janssen has implemented our recommendation and we find it acceptable. We have no additional comments or recommendations.
3.	The instruction for the patient to repeat the administration in alternating nostrils until the complete dose is administered is important information and may overlooked.	Step 4 of the IFU instructs the user to, "[REDACTED] (b) (4) : Switch hands to insert tip into the <b>second nostril</b> . Repeat Step 4 to deliver second spray." We note failures in the HF validation study included participant performance and subjective feedback regarding the IFU not being clear if the total contents from one device should be administered in the same nostril.	We recommend including the statement in Step 4, "Instruct patients to alternate nostrils for each spray until the complete dose has been administered." to minimize the risk for this instruction to be overlooked.	The Applicant proposes to maintain the current instruction in Step 4 because the revision contradicts the instruction in Step 5, specifically the instruction that if the HCP sees a green dot they should have the patient spray again in the second nostril. The FDA proposal to change the instruction for the patient to alternate nostrils for each spray could be confusing. A similar IFU was used in clinical studies, with over 10,000 proposed commercial devices with the visual indicator, and no complaints of delivering the total contents of a device into a single nostril were encountered. To	We disagree with Janssen's rationale for maintaining the current instruction in Step 4. They have cited clinical experience during clinical studies as part of their supporting rationale to maintain their instructions; however, clinical studies generally are not adequately representative of real world use. Failures were seen in their previous HF validation study indicating that there is still a risk for confusion regarding when to switch nostrils when administering this drug. Not completing this task correctly can

<b>Issue #</b>	<b>Identified Issue</b>	<b>Rationale for Concern</b>	<b>FDA Recommendation</b>	<b>Applicant Response</b>	<b>DMEPA Comment</b>
				<p>address the issue of clearly communicating that one device should be administered into each nostril and not the same nostril, the instruction has been included in multiple locations:</p> <ul style="list-style-type: none"> <li>• Product carton</li> <li>• IFU indicator graphic</li> <li>• IFU Step 4</li> </ul>	<p>lead to an underdose. Unlike the task of blowing the nose (see above), there may be a greater risk for underdose with this task since the consideration of whether a user is sick or has allergies is not relevant. We are open to other means to address this risk other than the specific wording change we previously recommended. For example, we note the information in the indicator graphic in the IFU states <i>“One device contains 2 sprays. (1 spray for each nostril).”</i> This statement can be made more prominent with the use of bolding. We provide a recommendation in Table 5.</p>
4.	The sub steps are not indented, numbered, bulleted or otherwise formatted for improved readability of the text.	Some of the sub steps may be overlooked without improved formatting of the text.	Consider the use of bulleting in order to improve the readability of the sub steps. As an example, consider the following bulleted format for Step 2:	The Applicant agrees to use bulleting in order to improve the readability of the sub steps.	Janssen has implemented our recommendation to add bullets and we find it acceptable.

**Table 2: Summary and Analyses of Janssen’s Responses**

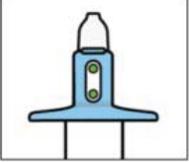
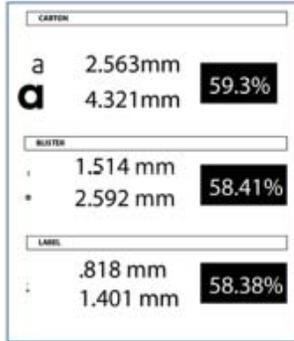
Issue #	Identified Issue	Rationale for Concern	FDA Recommendation	Applicant Response	DMEPA Comment
			<p><b>Step 2 Prepare device</b></p>  <p><b>Healthcare professional:</b></p> <ul style="list-style-type: none"> <li>• Check expiration date ("EXP"). If expired, get a new device.</li> <li>• Peel blister and remove device.</li> </ul>  <p><b>Healthcare professional:</b></p> <ul style="list-style-type: none"> <li>• <b>Do not prime device.</b> This will result in a loss of medication.</li> <li>• Check that indicator shows <b>2 green dots</b>. If not, dispose of device and get a new one.</li> <li>• Hand device to patient.</li> </ul>		<p>We also note that Janssen made a correction to the blister labeling by moving the arrow from the right side to the left side (see updated image below).</p>  <p>Therefore, to accommodate this change, the blister image in Step 2 of the IFU was revised to show how the blister appears when peeled from the left side (see updated image below).</p> 

Table 2: Summary and Analyses of Janssen's Responses																											
Issue #	Identified Issue	Rationale for Concern	FDA Recommendation	Applicant Response	DMEPA Comment																						
					We have no concerns with these changes and do not have any additional comments or recommendations related to these proposed changes.																						
<b>Comments for the Device Label, Blister Label, and Single Device Carton Labeling</b>																											
1.	The established name does not appear to be at least ½ the size of the proprietary name.	Lack of sufficient prominence of the established name may contribute to product selection medication errors.	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).	<p>The Applicant's practice is to typeset the established name at 60% of the height of the proprietary name to ensure that we met or exceed the requirement of 50%. Visually it may appear smaller due to the different font styles used. The graphic shown below designates the percentage of the established name to proprietary name as typeset on the Carton, Blister (foil) and Device Label.</p>  <table border="1" data-bbox="1291 1047 1585 1388"> <thead> <tr> <th>Category</th> <th>Character</th> <th>Height (mm)</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td rowspan="2">CARTON</td> <td>a</td> <td>2.563mm</td> <td rowspan="2">59.3%</td> </tr> <tr> <td>Q</td> <td>4.321mm</td> </tr> <tr> <td rowspan="2">BLISTER</td> <td>i</td> <td>1.514 mm</td> <td rowspan="2">58.41%</td> </tr> <tr> <td>*</td> <td>2.592 mm</td> </tr> <tr> <td rowspan="2">LABEL</td> <td>i</td> <td>.818 mm</td> <td rowspan="2">58.38%</td> </tr> <tr> <td>i</td> <td>1.401 mm</td> </tr> </tbody> </table>	Category	Character	Height (mm)	Percentage	CARTON	a	2.563mm	59.3%	Q	4.321mm	BLISTER	i	1.514 mm	58.41%	*	2.592 mm	LABEL	i	.818 mm	58.38%	i	1.401 mm	We acknowledge Janssen's explanation that the size of the established name meets the regulatory requirements. We have no additional recommendations or comments.
Category	Character	Height (mm)	Percentage																								
CARTON	a	2.563mm	59.3%																								
	Q	4.321mm																									
BLISTER	i	1.514 mm	58.41%																								
	*	2.592 mm																									
LABEL	i	.818 mm	58.38%																								
	i	1.401 mm																									

<b>Table 2: Summary and Analyses of Janssen's Responses</b>					
<b>Issue #</b>	<b>Identified Issue</b>	<b>Rationale for Concern</b>	<b>FDA Recommendation</b>	<b>Applicant Response</b>	<b>DMEPA Comment</b>
2.	As currently presented, the statement of strength is confusing because it does not state the number of milligrams delivered per spray or the number of sprays delivered by the device.	The statement of strength is confusing and may contribute to wrong dose medication errors.	Revise the statement of strength to include the number of milligrams delivered per spray and the number of sprays delivered by the device, as follows:  14 mg esketamine per spray  Device delivers 2 sprays (28 mg esketamine)	For the esketamine combination product, a single spray does not represent the minimum dose. The contents of the entire device, nominal 28 mg of esketamine, are required to deliver the minimum dose. As noted in Figure 1b, the redesigned carton submitted in Module 1 of the NDA clearly indicates 28 mg per device as prominent information to clarify how much drug is available per device (a), and adds total dose (c) to the dose area to increase clarity around the number of devices needed to achieve the correct dose. Therefore, the Applicant proposes to maintain the carton label as presented in Figure 1b.	We recognize that a single spray does not represent the minimum dose but it does represent information that is pertinent to HCPs in determining the number of sprays needed to deliver a specified dose. However, based on additional information provided by Janssen to the Office of Pharmaceutical Quality (OPQ), we were informed by OPQ that each spray may deliver an amount that varies from 14 mg but two sprays will deliver a total of 28 mg.  We disagree with Janssen's proposal to maintain the carton labeling as submitted in the NDA. The limited supplemental HF study results indicated there were 7 participants who experienced difficulty or near misses with correct carton selection and we find that additional

<b>Issue #</b>	<b>Identified Issue</b>	<b>Rationale for Concern</b>	<b>FDA Recommendation</b>	<b>Applicant Response</b>	<b>DMEPA Comment</b>
					revisions are needed to help mitigate potential confusion. In Table 5, we provide recommendations for improvements to the carton labeling as well as the blister labeling and device label.
3.	The proposed expiration date format is not indicated.	The proposed format for the expiration date is requested in order that we may determine whether it may be confusing and lead to deteriorated drug medication errors.	Indicate the proposed expiration date format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and nonzero day. FDA recommends that the expiration date appears in YYYY-MMDD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend	The expiration date is applied on the packaging components during production and cannot be seen in the Artwork Mockup (PDF). The Applicant intends to utilize a presentation in compliance with the recommendations.	We acknowledge Janssen’s intent to implement our recommendation and expect that the proposed format will be indicated on revised labels when submitted to the Agency. We provide a recommendation in Table 5 of this review to address our concern.

<b>Table 2: Summary and Analyses of Janssen's Responses</b>					
<b>Issue #</b>	<b>Identified Issue</b>	<b>Rationale for Concern</b>	<b>FDA Recommendation</b>	<b>Applicant Response</b>	<b>DMEPA Comment</b>
			that a hyphen or a space be used to separate the portions of the expiration date.		
<b>Packaging</b>					
1.	Your currently proposed packaging (i.e., cartons containing 1, 2, or 3 devices) may be confusing because it may not be clear which package should be selected for a particular dose or that all of the devices in a particular package should be used.	<p>The proposed packaging may contribute to product selection medication errors and potential wrong dose errors.</p> <p>Based on the results from your HF validation study, it was unclear to users that the number of devices per carton is dose specific. There is also a risk that if the dose specific carton needed is not on hand, an individual device(s) may be removed from a multidevice carton, which may lead to further confusion.</p>	Consider marketing a single package configuration for your product (i.e., one device per carton). This may help to minimize potential product selection errors. We recommend that you conduct another HF validation study and use a single device per package configuration in the study. Also, the study should assess whether healthcare providers can select the correct number of devices to obtain for a specified dose.	The carton label modifications, submitted in Module 1 of the NDA and described in the response to Question 1A were shown to effectively minimize potential product selection errors. A supplemental HF study with thirty participants (fifteen per user group) demonstrated that healthcare providers can select the correct number of devices to obtain the prescribed dose and would self-correct to the prescribed dose and devices if there was hesitation or confusion. While we cannot prevent users from opening multi-device packs for individual devices, this would have to be addressed locally under prescription controls and controlled substances procedures. As the device contains a controlled substance, patients will	We have become aware of new information from the Division of Psychiatry Products (DPP) that the Spravato 28 mg dose will not be an approved dose for this product and that only the 56 mg and 84 mg doses will be approved. In light of these new considerations, our previous recommendation for a single carton configuration no longer applies and would be error prone given the lack of consistency with the labeled dosing for this product when the 28 mg dose is removed from labeling. We propose that only the Spravato 56 mg and 84 mg carton packaging should be marketed. We provide a recommendation in

<b>Table 2: Summary and Analyses of Janssen's Responses</b>					
<b>Issue #</b>	<b>Identified Issue</b>	<b>Rationale for Concern</b>	<b>FDA Recommendation</b>	<b>Applicant Response</b>	<b>DMEPA Comment</b>
				<p>always receive only the prescribed dose and the number of devices selected should be controlled. Our approach to packaging and labeling, where multiple unit doses from multiple devices are required, is consistent with other products with multiple pre-filled device packaging such as the AbbVie HUMIRA® Pen (3 single-use pens per carton), Adapt Pharma's NARCAN® Nasal Spray (2-pack), GSK's Imitrex® Nasal Spray (box of 6 nasal spray devices), Novartis's COSENTYX® (unit packs of 1 or 2 PFS and multipacks of 6 PFS) and Lilly's Taltz® (1, 2, or 3 pack of PFS or autoinjectors)</p>	<p>Table 4 to address our concern.</p>

### 3.2 SUPPLEMENTAL HUMAN FACTORS STUDY RESULTS AND ANALYSES

Janssen submitted supplemental HF study on January 30, 2019 stating that the objective of the supplemental HF study was to validate the carton labeling changes they made to mitigate the use error observed in the HF validation study submitted on September 4, 2018.

#### ***Overview of the supplemental HF study***

The supplemental HF study consisted of two user groups, 15 pharmacists/pharmacy techs and 15 nurses. The user groups completed the following tasks:

Pharmacist/pharmacy tech:

- Task 1: The pharmacist/pharmacy tech was given a prescription for one (1) of the three (3) doses of the Product (28 mg, 56 mg, or 84 mg). They selected the Product from the cartons displayed on the shelving unit. The pharmacist/pharmacy tech then determined the dosage (of each individual device and the devices in total) and the number of devices in the selected Product carton.
- Tasks 2 & 3: The pharmacist/pharmacy tech determined the dosage (of each individual device and the devices in total) and the number of devices in the two (2) remaining Product cartons.

Nurse:

- Task 1: The nurse was given one (1) of the three (3) Product cartons with the correct corresponding prescription. They then determined whether or not they had been supplied with the correct dosage/number of devices.
- Tasks 2 & 3: The nurse determined the dosage (of each individual intranasal device and the devices in total) and the number of devices in the two (2) remaining Product cartons.

#### ***Supplemental HF study Results***

In Table 3, Janssen's summary of the supplemental HF study results, we also provide our analyses and recommendations regarding the 7 close calls/difficulties observed in the study. These close calls/difficulties occurred with packages containing multiple devices. Although the study report states the participants were able to recover, we are concerned that they found the carton labeling confusing and that Janssen did not propose any mitigations.

Additionally, this study did not assess whether HCPs and patients can follow the instructions for use and administer a correct dose as was done in the previous HF study. Thus, it is unclear how users would perform if required to administer a correct dose when presented with the proposed carton labeling.

<b>Table 3. Summary and Analyses of Supplemental Human Factors Study Report</b>						
<b>Task</b>	<b>Number of Use Errors (I)</b>	<b>Number of Close Calls and Use Difficulties (R)</b>	<b>Description of Use Errors/Close Calls/Use Difficulties (e.g. Issues)</b>	<b>Janssen’s Root Cause Analysis</b>	<b>Janssen’s Mitigation Strategy</b>	<b>DMEPA’s Analyses and Recommendations</b>
Identify correct number of devices needed to administer prescribed dose	0	0 (for 28mg)	n/a	n/a	n/a	n/a
	0	3 (for 56 mg)	Two HCPs filled their assigned prescription with a different carton configuration than intended but achieved the correct dose and self-corrected after reviewing the carton label	Both HCPs indicated that they only saw the 28 mg label and were initially confused by multiple doses in a single carton but after reading the label, they were able to see that each device was single use	No use errors occurred as a result of the carton label change. Likelihood of this use error has been reduced as far as possible; no further labeling mitigations are feasible or likely to enhance performance. Product familiarization would be an effective mitigation.	The statement “28 mg per device” is very prominent on all of the proposed carton labeling (carton containing 1 device, 2 devices, and 3 devices) and may lead to confusion when trying to determine the number of devices contained in the carton or the dose that the carton contains. The prominence of the statement may lead to product selection errors (as shown in the study) and wrong dose medication errors as well. Janssen has not proposed any mitigations.  Based on the root cause analysis, we recommend the total dose statement be made more prominent than the 28 mg per device statement. This should help HCPs more easily determine that they have the correct carton

**Table 3. Summary and Analyses of Supplemental Human Factors Study Report**

Task	Number of Use Errors (I)	Number of Close Calls and Use Difficulties (R)	Description of Use Errors/Close Calls/Use Difficulties (e.g. Issues)	Janssen’s Root Cause Analysis	Janssen’s Mitigation Strategy	DMEPA’s Analyses and Recommendations
			One HCP was able to select the correct carton but was unsure about the number of devices in the carton. The HCP was able to confirm the number of devices after opening the carton.	The HCP was not familiar with using multiple devices for a single dose which prompted them to open the carton to confirm the contents.		based on the prescribed dose. See Table 5 for our recommendations.
			Two HCPs initially answered that each carton contained one device with different doses but were able to correct their answer after reviewing the carton label.	The HCPs attributed their error to being unfamiliar with using multiple single-use devices and more familiar with multi-use nasal sprays.		The presentation of information on the principal display panel of the carton labeling is not optimized to prevent confusion. Additionally, unfamiliarity with using multiple single-use nasal spray devices to administer a single dose may contribute to confusion as well. Janssen has not proposed any mitigations. See Table 5 for our recommendations.
			One HCP initially selected the incorrect carton(s) to fill the assigned prescription,	The HCP reported that she was not familiar with using more than one device for a dose and		The prominence of the statement “28 mg per device” across all of the carton labeling is confusing and may lead to wrong dose

<b>Table 3. Summary and Analyses of Supplemental Human Factors Study Report</b>						
<b>Task</b>	<b>Number of Use Errors (I)</b>	<b>Number of Close Calls and Use Difficulties (R)</b>	<b>Description of Use Errors/Close Calls/Use Difficulties (e.g. Issues)</b>	<b>Janssen’s Root Cause Analysis</b>	<b>Janssen’s Mitigation Strategy</b>	<b>DMEPA’s Analyses and Recommendations</b>
			selecting three 84-mg cartons to fill an 84 mg prescription before self-correcting and selecting one 84 mg carton.	noted that seeing “28 mg” on each carton caused her to select three 84 mg cartons		errors. Janssen has not proposed any mitigations. See Table 5 for our recommendations.
			One HCP was able to select the correct carton but was unsure about the number of devices in the carton. The HCP was able to confirm the number for devices after opening the carton.	The HCP was not familiar with using multiple devices for a single dose which lead them to open the carton to confirm the contents.		The presentation of information on the principal display panel of the carton labeling is not optimized to prevent confusion. Additionally, unfamiliarity with using multiple nasal spray devices to administer a single dose may contribute to confusion as well. Janssen has not proposed any mitigations. See Table 5 for our recommendations.

### **3.3 LABEL AND LABELING**

The supplemental human factors study data indicate the proposed labeling alone are insufficient in informing users that the 56 mg dose and 84 mg dose require administration of multiple devices to obtain the required dose. We identified areas where improvements to the presentation and layout of information on the carton labeling, blister labeling, and device label are needed to help minimize the risk for medication error. Table 4 and Table 5 contain our recommendations.

Note that in our review of the previous HF validation study, we determined additional risk mitigations were necessary and we recommended that Janssen implement additional risk mitigations, including recommendations from the FDA, and conduct another HF validation study to demonstrate the effectiveness of those mitigations. However, in their response, Janssen stated they conducted a supplemental HF study and validated their proposed carton labeling so another HF validation study is not necessary. Given the results submitted and the fact that the supplemental study was limited in scope and did not fully evaluate all changes to the user interface, we have determined that the user interface, including the proposed carton labeling, has not demonstrated that it supports the safe and effective use of this product. However, in this particular circumstance, given the public health need for this product and the compressed remaining timeline available for this review cycle, we will provide our label and labeling recommendations with the intent to further reduce residual risk, and we will monitor postmarket for usability and medication error issues that arise regarding this product.

### **3.4 ASSESSMENT OF PACKAGING**

Janssen proposes the product be supplied in a carton containing one 28 mg nasal spray device (28 mg total dose), a carton containing two 28 mg nasal spray devices (56 mg total dose), and a carton containing three 28 mg nasal spray devices (84 mg total dose). However, because the 28 mg dose will not be approved, we propose that only the 56 mg and 84 mg packaging be approved in order to minimize the potential for product selection and wrong dose errors. Table 4 contains our recommendations.

### **3.5 ADDITIONAL COMMENTS**

This product may be confusing for some users given that multiple single-use nasal devices are required in order to administer a single dose. Some of the study participant feedback from the supplemental human factors study indicated that some HCPs are unfamiliar with this type of packaging and dose administration. Therefore, to help familiarize HCPs with the product, its packaging and how it's administered, we recommend that Janssen launches an educational campaign and communication plan to inform HCPs about the product. Table 5 contains our recommendation.

## **4 CONCLUSION & RECOMMENDATIONS**

Janssen's written responses, dated January 30, 2019, submitted in response to our recommendations dated January 17, 2019, do not adequately address our concerns. Thus, we

maintain our conclusion that the human factors data does not provide sufficient evidence to demonstrate that the proposed product can be used safely and effectively by the intended users for its intended uses and use environments.

The supplemental human factors study results observed several use difficulties with packages containing multiple devices. The results did not demonstrate that confusion with the carton labeling has been appropriately mitigated. Additionally, the study did not adequately evaluate whether health care providers and patients can follow the instructions for use and administer a correct dose.

The human factors data indicate the current labeling strategies alone are insufficient in informing users that a 56 mg dose and 84 mg dose require administration of multiple devices to obtain the required dose. Thus, we determined that additional improvements should be made to the user interface to further mitigate the risk for medication errors to occur with the use of the product. In addition, our review of the label and labeling identified areas where the proposed label and labeling are vulnerable to medication errors. We provide recommendations for the Division in Table 4, below, and recommendations for Janssen in Table 5. We ask that the Division consider our recommendations in Table 4 and convey those recommendations to Janssen. We also request that the Division convey Table 5 in its entirety to Janssen.

<b>Table 4: Identified Issues and Recommendations for the Division of Psychiatry Products</b>			
	<b>Identified Issue</b>	<b>Rationale for Concern</b>	<b>Recommendation</b>
<b>Instructions for Use (IFU)</b>			
1.	The IFU contains information related to administering a 28 mg dose. However, it is our understanding that the Division does not plan to approve the 28 mg dose. Thus, the IFU is not consistent with the PI.	Having information in the IFU related to an unapproved dose may lead to confusion and wrong dose medication errors.	We recommend the removal all information in the IFU related to the 28 mg dose. Specifically, (b) (6) .
<b>Packaging</b>			
1.	It is our understanding that the Division does not plan to approve the 28 mg dose. Thus, the proposed 28 mg carton packaging does not represent a dose for this product.	We are concerned that having a packaging configuration that does not represent a proposed dose for this product may lead to product selection and wrong dose medication errors.	We recommend that Janssen only provide the packaging that is representative of the approved doses for this product (i.e., 56 mg and 84 mg).

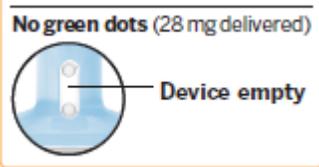
#### **4.1 RECOMMENDATIONS FOR JANSSEN**

Our review of your supplemental human factors study results concluded that the human factors data does not provide sufficient evidence to demonstrate that Spravato can be used safely and effectively by the intended users for its intended uses and use environments.

We are concerned that seven participants in the supplemental human factors study you submitted on January 30, 2019, experienced a difficulty or near miss in identifying the correct carton that contained the number of devices needed to administer the prescribed dose. The results did not demonstrate that you have mitigated the risk of confusion with the carton labeling to an acceptable level. Based on our evaluation, we have identified areas where the product label and labeling can be improved to minimize the risk for medication errors. Please see the following table *Identified Issues and Recommendations for Janssen* which contains our recommendations.

<b>Table 5: Identified Issues and Recommendations for Janssen (entire table to be conveyed to Janssen)</b>			
	<b>Identified Issue</b>	<b>Rationale for Concern</b>	<b>Recommendation</b>
<b>Instructions for Use (IFU)</b>			
1.	The IFU does not make it immediately clear “up front” that the device delivers two sprays that are equivalent to 28 mg.	Not having this information presented at the very beginning of the IFU may lead to confusion concerning the contents of the device. However, having this information there may help to reinforce information concerning the device contents and the amount of sprays and drug delivered, thus, helping to minimize confusion about what is contained in the device.	Under the “Nasal Spray Device” diagram, add the following statement: “Each device administers two sprays delivering a total of 28 mg of esketamine”
2.	Instructions to alternate nostrils when using the device is important and should not be overlooked.	Failures in the previous HF validation study included participant performance and subjective feedback regarding the IFU not being clear on whether the total contents from one device should be administered in the same nostril.	To bring additional prominence to this information, we recommend the statement “One device contains 2 sprays (1 spray for each nostril)”, located in the Indicator graphic, be made more prominent through the use of a bold font and/or other means.
3.	The illustration at the bottom of the “Indicator” graphic may be confusing because it does not clearly indicate that	Lack of clear understanding of the relationship between the dots and number of sprays administered could potentially lead to wrong dose errors.	In the illustration pictured below, keep the statements “No green dots” and “Device empty” and revise the “(28 mg delivered)” to read “Two sprays (28mg) delivered”.

**Table 5: Identified Issues and Recommendations for Janssen (entire table to be conveyed to Janssen)**

	Identified Issue	Rationale for Concern	Recommendation
	when no green dots are present that two sprays have been delivered.		
<b>Device Label</b>			
1.	The device label does not indicate the number of sprays that the device delivers.	Failure to recognize that the device delivers 2 sprays may lead to underdose medication errors.	<p>We recommend you incorporate the following format and wording on the principal display panel (PDP) to indicate the number of sprays delivered by the device:</p> <div style="border: 1px solid black; padding: 10px; text-align: center;"> <p><b>Spravato</b>                      (esketamine) nasal spray  <b>28 mg per device</b>                      Each device delivers two sprays                      containing a total of 28 mg of esketamine</p> </div>
2.	The NDC number is not indicated on the label.	The NDC number useful for helping to correctly identify products.	We request that you add the NDC number to the PDP per 21 CFR 201.2.
<b>Blister Labeling</b>			
1.	The blister labeling does not indicate the number of sprays that the device delivers.	Failure to recognize that the device delivers 2 sprays may lead to underdose medication errors.	<p>We recommend you incorporate the following format and wording on the principal display panel (PDP) to indicate the number of sprays delivered by the device:</p> <div style="border: 1px solid black; padding: 10px; text-align: center;"> <p><b>Spravato</b>                      (esketamine) nasal spray  <b>28 mg per device</b>                      Each device delivers two sprays                      containing a total of 28 mg of esketamine</p> </div>

**Table 5: Identified Issues and Recommendations for Janssen (entire table to be conveyed to Janssen)**

	Identified Issue	Rationale for Concern	Recommendation
			Additionally, in order to help ensure that this information is the most prominent, we recommend that you delete the <span style="background-color: #cccccc;">(b) (4)</span>
2.	The NDC number is not indicated on the blister labeling.	The NDC number useful for helping to correctly identify products.	We request that you add the NDC number to the PDP per 21 CFR 201.2.
<b>Carton Labeling</b>			
1.	As proposed, the carton labeling is confusing and may lead to product selection and wrong dose medication errors.	The supplemental HF study results indicated difficulties and near misses occurred when selecting the correct carton or determining the number of devices contained in the carton. Based on participant feedback, the prominence of the statement <span style="background-color: #cccccc;">(b) (6)</span> across all of the carton labeling led to some of the confusion. We are concerned that product selection and wrong dose errors may occur with the proposed carton labeling and find that additional mitigations are needed to help mitigate potential confusion.	We recommend you incorporate the following format on the principle display panel (PDP) of the carton labeling to help mitigate product selection and wrong dose errors. Revise the 84 mg carton labeling accordingly. <div style="border: 1px solid black; padding: 10px; margin: 10px auto; width: fit-content;"> <p style="text-align: center;"><b>Spravato</b> (esketamine) nasal spray</p> <p style="text-align: center;"><b>56 mg Kit</b></p> <p style="text-align: center;">Contents: Two Spravato 28 mg devices</p> <p style="text-align: center; color: red;">Each device delivers two sprays containing a total of 28 mg of esketamine</p> <p style="text-align: center;">56 mg dose=2 devices (4 sprays)</p> </div>
<b>General Comment for the device label, blister labeling and all carton labeling</b>			
1.	The proposed format for the	The proposed format for the expiration date is requested in	This is a recommendation from our previous review. You responded that you intend to utilize a presentation in

<b>Table 5: Identified Issues and Recommendations for Janssen (entire table to be conveyed to Janssen)</b>			
	<b>Identified Issue</b>	<b>Rationale for Concern</b>	<b>Recommendation</b>
	expiration date is not indicated.	order that we may determine whether it may be confusing and led to deteriorated drug medication errors.	compliance with that recommendation. On the label and labeling we request that you indicate the format you intend to use.
<b>General Recommendation</b>			
	<ul style="list-style-type: none"> <li>Based on the narratives from the HF validation study and the supplemental human factors study, some HCPs indicated they are unfamiliar with the type of packaging and dose administration that you have proposed (i.e., using multiple single-use nasal devices to administer a prescribed dose). Therefore, to help familiarize HCPs with the product, its packaging and how it's administered, we recommend that you consider launching an educational campaign and communication plan to inform HCPs about the product and its use.</li> </ul>		

**APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED**

**APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 3 presents relevant product information for Spravato received on November 20, 2018 from Janssen Pharmaceuticals, Inc.

<b>Table 3. Relevant Product Information</b>					
<b>Initial Approval Date</b>	N/A				
<b>Therapeutic Drug Class or New Drug Class</b>	Glutamate receptor modulator				
<b>Active Ingredient (Drug or Biologic)</b>	Esketamine				
<b>Indication</b>	Treatment-resistant depression (TRD)				
<b>Route of Administration</b>	Nasal				
<b>Dosage Form</b>	Nasal Spray				
<b>Strength</b>	28 mg esketamine per device (equivalent to 32.3 mg of esketamine hydrochloride)				
<b>Dose and Frequency</b>	<table border="1"> <thead> <tr> <th><b>Induction Phase (weeks 1-4)</b></th> <th><b>Maintenance Phase</b></th> </tr> </thead> <tbody> <tr> <td>Two treatment sessions/week: Starting Day 1 dose*: 56 mg Subsequent doses: 56 mg or 84 mg</td> <td><b>Weeks 5-8:</b> 56 mg or 84 mg once weekly <b>From Week 9:</b> 56 mg or 84 mg every 2 weeks or once weekly**</td> </tr> </tbody> </table> <p>* Patients ≥65 years Day 1 starting dose is 28 mg ** Lowest frequency to maintain remission/response.</p>	<b>Induction Phase (weeks 1-4)</b>	<b>Maintenance Phase</b>	Two treatment sessions/week: Starting Day 1 dose*: 56 mg Subsequent doses: 56 mg or 84 mg	<b>Weeks 5-8:</b> 56 mg or 84 mg once weekly <b>From Week 9:</b> 56 mg or 84 mg every 2 weeks or once weekly**
<b>Induction Phase (weeks 1-4)</b>	<b>Maintenance Phase</b>				
Two treatment sessions/week: Starting Day 1 dose*: 56 mg Subsequent doses: 56 mg or 84 mg	<b>Weeks 5-8:</b> 56 mg or 84 mg once weekly <b>From Week 9:</b> 56 mg or 84 mg every 2 weeks or once weekly**				
<b>How Supplied</b>	<p>Spravato nasal spray 28 mg is provided in a unit dose nasal spray device packaged in a sealed blister.</p> <p>Spravato will be available in the following presentations:</p> <ul style="list-style-type: none"> <li>• Carton containing one 28 mg nasal spray device (28 mg total dose)</li> <li>• Carton containing two 28 mg nasal spray devices (56 mg total dose)</li> <li>• Carton containing three 28 mg nasal spray devices (84 mg total dose)</li> </ul> <p>Within each pack, each device is individually packaged in a sealed blister.</p>				
<b>Storage</b>	Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].				
<b>Intended Users</b>	<ul style="list-style-type: none"> <li>• Patients diagnosed with MDD, 18+ years of age</li> <li>• Healthcare providers (nurses and psychiatrists), 18+ years of age, who regularly treat and administer medication to patients diagnosed with depression.</li> </ul>				
<b>Intended Use Environment</b>	Hospital or clinic under the supervision of a healthcare provider				

## **APPENDIX B. BACKGROUND INFORMATION**

### **B.1 PREVIOUS HF REVIEWS**

#### **B.1.1 Methods**

On February 20, 2019, we searched FDA previous reviews using the terms, esketamine, to identify reviews previously performed by DMEPA or CDRH.

#### **B.1.2 Results**

Our search identified two previous reviews<sup>d,e</sup> and we confirmed that our previous recommendations were implemented or considered.

## **APPENDIX C. JANSSEN'S RESPONSES TO RECOMMENDATIONS MADE IN OUR PREVIOUS HUMAN FACTORS (HF) RESULTS AND LABELS AND LABELING REVIEW**

Janssen's responses is accessible in EDR via this link:

<\\cdsesub1\evsprod\nda211243\0038\m1\us\response-to-fda-24jan2019.pdf>

## **APPENDIX D. SUPPLEMENTAL HF STUDY RESULTS REPORT**

The supplemental HF study results report is accessible in EDR via this link:

<\\cdsesub1\evsprod\nda211243\0038\m1\us\ds-tec-140305.pdf>

## **APPENDIX E. LABEL AND LABELING**

### **E.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>f</sup> along with postmarket medication error data, we reviewed the following Spravato labels and labeling submitted by Janssen Pharmaceuticals, Inc.

- Device label received on September 4, 2018
- Carton labeling received on September 4, 2018
- Blister labeling received on January 30, 2019

---

<sup>d</sup> Holmes, L. Human Factors Protocol Review for Esketamine IND 114345. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Aug 19. RCM No.: 2016-1230.

<sup>e</sup> Garrison, N and Holmes, L. Human Factors Results and Labels and Labeling Review for Spravato NDA 211243. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jan 14. RCM No.: 2018-1875 and 2018-1873.

<sup>f</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Instructions for Use received on January 30, 2019 (image not shown), accessible at: <\\cdsesub1\evsprod\nda211243\0038\m1\us\draft-label-text-spravato-28mg-device-np-sol-ifu-pic.pdf>

## **E.2 Label and Labeling Images (not to scale)**

### **Device Label**



### **Blister Labeling**



---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/

---

LORETTA HOLMES  
02/28/2019 05:23:22 PM

SEVAN H KOLEJIAN  
02/28/2019 05:25:37 PM

IRENE Z CHAN  
03/01/2019 09:41:57 AM

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** March 1, 2019

**To:** Jean S. Kim, M.D., Clinical Reviewer  
Division of Psychiatry Products (DPP)

Hiren Patel, PharmD, Regulatory Project Manager, (DPP)

Kimberly Updegraff, PharmD, Associate Director for Labeling, (DPP)

**From:** Domenic D'Alessandro, PharmD, MBA, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Aline Moukhtara, RN, MPH, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for SPRAVATO™ (esketamine) nasal spray, CIII

**NDA:** 211243

---

In response to DPP consult request dated September 5, 2018, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), Medication Guide, and carton and container labeling for the original NDA submission for SPRAVATO™ (esketamine) nasal spray, CIII.

**PI:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP (Hiren Patel) on February 27, 2019, and are provided below.

**IFU:** OPDP has reviewed the attached proposed IFU submitted by the Sponsor to the electronic document room (EDR) on January 30, 2019, and we do not have any comments.

**Medication Guide:** A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on February 25, 2019.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the EDR on January 30, 2019, and our comment is provided below.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro (301) 796-3316 or [domenic.dalessandro@fda.hhs.gov](mailto:domenic.dalessandro@fda.hhs.gov).

77 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

DOMENIC G DALESSANDRO  
03/01/2019 10:20:53 AM



## MEMORANDUM

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

**Date:** March 1, 2019

**To:** Tiffany Farchione, MD, Director (Acting)  
Division of Psychiatry Products

**Through:** Dominic Chiapperino, PhD, Director  
Silvia Calderon, PhD, Senior Pharmacologist  
Controlled Substance Staff

**From:** Martin Rusinowitz, MD, Senior Medical Officer  
Jovita Randall-Thompson, PhD, Pharmacologist  
Controlled Substance Staff

**Subject:** **Spravato, NDA 211243**  
**Generic Name:** esketamine (or JNJ-54135419-AAC, formulation # JNJ-54135419-AAC-G005)  
**Dosages:** 56 and 84 mg of esketamine (base)  
**Formulation:** Intranasal spray containing an aqueous solution of esketamine HCl, at a concentration 161.4 mg/mL, equivalent to 140.0 mg/mL esketamine base, in water; each single-use device delivers two individual sprays dispensing a total volume of 0.2 mL of drug product, equivalent to 32.3 mg of esketamine HCl  
**IND Number:** 114345  
**Indication:** Treatment Resistant Depression (TRD)  
**Sponsor:** Janssen Pharmaceuticals, Inc. (Subsidiary of Johnson and Johnson)  
**PDUFA Goal Date:** March 3, 2019

### Materials Reviewed:

- NDA 211243, eCTD 0001, submitted September 4, 2018
- Abuse Potential Assessment, JNJ-54135419 (esketamine)
- A Single-Center, Single-Dose, Double-Blind, Double-Dummy, Placebo-Controlled, Randomized Crossover Study to Evaluate the Abuse Potential of Intranasal Esketamine Compared to Racemic Intravenous Ketamine in Nondependent, Recreational Users of Perception-Altering Drugs, Report 54135419TRD1015 (Phase 1, human abuse potential study)
- In vitro Safety Pharmacology Report 100006490, 100030089\_FK12073, 100030089\_FK1272, 100030088\_FK12075, and 100002086
- Phase 2 Study Reports ESKETIVTRD-2001, and -2003; 54135419TRD2005; and ESKETINSUI2001
- Phase 3 Study Reports ESKETINTRD-3001, -3002, -3003, -3004, and -3005; 54135419SUI-3001, and -3002; and 54135419TRD3008

Table of Contents

I. SUMMARY2

1. Background.....2

2. Conclusions.....3

3. Recommendations.....5

II. DISCUSSION.....5

1. Chemistry.....6

1.1. Drug Substance.....6

1.2. Drug Product.....6

2. Nonclinical Pharmacology.....7

2.1. Receptor Binding and Functional Assays.....7

2.2. Findings from Safety Pharmacology and Toxicology Studies.....8

2.3. Animal Behavioral Studies.....10

2.4. Tolerance and Physical Dependence Studies in Animals.....10

3. Clinical Pharmacology.....11

3.1. Absorption, Distribution, Metabolism, Elimination (ADME).....11

4. Clinical Studies.....12

4.1. Overview.....12

4.2. Human Abuse Potential Study.....13

4.3. Adverse Event Profile Through all Phases of Development.....22

4.4. Safety Profile.....24

4.5. Evidence of Abuse, Misuse and Diversion in Clinical Trials.....25

4.6. Physical Dependence Studies in Humans.....25

5. Regulatory Issues and Assessment.....26

6. Other Relevant Information.....27

III. REFERENCES.....27

**I. SUMMARY**

**1. Background**

This memorandum responds to a consult request dated September 5, 2018 from the Division of Psychiatry Products (DPP) regarding esketamine, trade name Spravato (IND 114345 and NDA 211243).

Esketamine, the (S)-enantiomer of ketamine, is a Schedule III (C-III) substance under the Controlled Substance Act (CSA) in accordance with 21CFR1308.13(c)(7). Therefore, esketamine and products that

contain the substance are also controlled in C-III. Janssen Pharmaceuticals (Sponsor) has submitted a new drug application (NDA) for esketamine to be administered intranasally (IN) by patients diagnosed with treatment-resistant depressive disorder (TRD), which was granted Breakthrough Therapy designation on November 7, 2013 (also for Major Depressive Disorder with imminent risk for suicide, IND (b) (4) granted August 9, 2016).

Ketamine in racemic form is approved and marketed in the United States as Ketalar solution for injection (under NDA 016812). Esketamine is marketed in other countries as a general anesthetic (Vesierra, Ketanest, and Ketanest-S injectable solutions [5 and 25 mg base/mL]). However, the proposed esketamine formulation under current pending NDA 211243 would be the first esketamine formulation approved in the United States. All marketed esketamine and ketamine products are formulated as injectable solutions [intravenous (IV) or intramuscular (IM)] for human and animal use.

Esketamine, like ketamine, is a non-competitive N-methyl-D-aspartate (NMDA) glutamate-receptor antagonist. Its use is associated with abuse-related effects such a dissociative, psychedelic/hallucinogenic properties for which ketamine is often abused.<sup>1</sup>

Ketamine that is used recreationally is mostly diverted from hospitals, veterinary clinics or the pharmaceutical distribution network. The most popular abuse form for ketamine is a powder, which is snorted. The powder is prepared by evaporation of the injectable solution.

CSS recommended that the Sponsor conduct a human abuse potential (HAP) study (CSS Review by Dr. Rusinowitz, DARRTS October 20, 2015; Type B meeting minutes, DARRTS July 3, 2014), because esketamine is the S-enantiomer of racemic ketamine and its pharmacodynamics (PD), including abuse potential, may not be the same as racemic ketamine. Nonclinical abuse potential studies were not recommended. The Sponsor conducted HAP Study #54135419TRD1015.

## 2. Conclusions

1. Racemic ketamine (*R,S*), commonly known as ketamine, is a mixture composed of equal amounts of two optical isomers identified as (*S*)-ketamine or esketamine and (*R*)-ketamine also known as arketamine.<sup>2</sup>

Esketamine is a controlled substance in Schedule III of the Controlled Substance Act (CSA), as ketamine, its salts, isomers and salts of isomers are Schedule III substances under the CSA [21 CFR 1308.13 (c)(7)]. The Sponsor did not request a scheduling change for esketamine.

2. Esketamine and ketamine show a qualitatively similar pharmacological binding profile, suggesting that esketamine and ketamine will mediate similar effects.

---

<sup>1</sup> Vollenweidera FX, Leendersb KL, Øyec I, Hella D, and Angsta J. Differential psychopathology and patterns of cerebral glucose utilization produced by (*S*)- and (*R*)-ketamine in healthy volunteers using positron emission tomography (PET). *European Neuropsychopharmacology*. 1997; 7: 25–38.

<sup>2</sup> Ketamine has one asymmetric carbon and therefore may exist in two forms, the (*S*) and the (*R*) enantiomers. The (*S*) and (*R*) prefix refers to the absolute configuration of the enantiomer. Enantiomers also are described as (+) or (-) or by the prefix dextro or levo.

3. Ketamine, esketamine, and arketamine are selective for the NMDA receptor with  $K_i$ -values in the micromolar range. Esketamine and ketamine differ in their binding affinity at the NMDA receptor, and these differences may explain drug potency differences. For example, based on assessments conducted by the Sponsor, the affinity of esketamine for the NMDA receptor is approximately 1.5- to 2.8-fold higher than that of ketamine and 4-fold higher than that of arketamine. Therefore, it may be concluded that esketamine's potency as an NMDA receptor antagonist is higher, and less of the drug would be needed to activate these receptors to produce comparable effects as racemic ketamine.
4. The Sponsor did not conduct nonclinical behavioral studies to characterize the reinforcing, discriminative properties, and physical dependence properties of esketamine. The Sponsor relied on published drug discrimination and self-administration studies conducted with ketamine. Esketamine is an enantiomer of ketamine and, as such, preclinical abuse findings reported with ketamine are considered as predictive of likely abuse-related effects that would be found with esketamine. Ketamine has been shown to be self-administered and therefore reinforcing, as shown in animal self-administration studies, and is shown to generalize to PCP (Schedule II drug) when using a drug discrimination procedure, all signals of abuse potential. These findings predict that esketamine has abuse potential as well, but FDA found it acceptable for the Sponsor to conduct only a human abuse potential study, and not conduct preclinical studies with esketamine.
5. In a clinical study of abuse potential conducted in recreational polydrug recreational users (N=34) who had used at least two types of perception-altering drugs within three months prior to the study and reported use of racemic ketamine at least once in their lifetime, mean "Drug Liking at the Moment" and "Take Drug Again" scores for single doses of esketamine nasal spray (84 mg and 112 mg) were no different from the positive control drug, intravenous ketamine (0.5 mg/kg infused over 40 minutes), and were greater than scores from placebo.
6. The highest dose of intranasal esketamine (112 mg) differentiated from the lower intranasal esketamine dose and from intravenous ketamine in that it was associated with much higher scores for "Hallucinating," "Floating," "Detached," and "Spaced Out" measures at one hour postdose.

There were no statistically significant differences in means between IN esketamine 84 mg and IV racemic ketamine for  $E_{max}$  "Hallucinating", "Floating", "Detached" and "Spaced out". The observed increases in perceptual effects associated with the higher dose of IN esketamine suggests, that as seen in prior studies conducted with IV ketamine (Bowdle et al., 1998), there may be a linear relation between the perceptual effects and plasma concentrations of the drug. If this is the case, a higher incidence of perceptual effects may be expected at higher than the maximum recommended doses.

7. The abuse-related adverse events (AEs) reported with esketamine are similar to those seen with ketamine. These include, in order of frequency, dissociation, somnolence, feeling drunk, and euphoria. There are no quantitative comparisons between racemic ketamine and esketamine, but the literature supports great similarity, albeit confounded by different dosages and indications.

8. All FDA approved ketamine products thus far are injectable anesthetic solutions administered IV or IM. Ketamine use is mainly restricted to hospital/clinic and veterinary settings. It is likely that an IN dosage form of esketamine may have an increased risk of abuse in that this dosage form may be more convenient to self-administer.

### 3. Recommendations

1. Esketamine, as an enantiomer of racemic ketamine, is a controlled substance in Schedule III of the Controlled Substance Act, within the definition of 21 CFR 1308.13(c)(7) for Schedule III "...ketamine, its salts, isomers, and salts of isomers...". No recommendation for a scheduling change is proposed or warranted for esketamine.
2. In order to mitigate risks of abuse and misuse of esketamine for this new dosage form and new indication (relative to FDA-approved ketamine products), a risk evaluation and mitigation strategy (REMS) will be required should this esketamine product be approved. The REMS will ensure that this esketamine product will not be dispensed to patients directly, with distribution restricted to specific clinical settings.
3. Labeling is currently being negotiated with the Sponsor and CSS is making recommendations that addresses some of the content in the Boxed Warning, section 5 Warnings and Precautions, and section 9 Drug Abuse and Dependence.

## II. DISCUSSION

Intranasal esketamine's proposed dosages are 56 and 84 mg (base). The drug will be administered in a supervised clinical setting to patients with treatment-resistant major depressive disorder (TRD). The esketamine nasal spray will be administered in conjunction with an oral antidepressant.

Ketamine is a racemic mixture consisting of equal amounts of two enantiomers, the S(+)-ketamine and R(-)-ketamine.

There is evidence that glutamate pathways are involved in the pathophysiology of depression that has led to ketamine's use as an antidepressant. Subanesthetic infusions of ketamine (0.5 mg/kg over 40 minutes) demonstrated same day antidepressant effects in patients who had responded poorly to conventional antidepressant drugs. This response lasted for a few days<sup>3</sup>. The United States Prescribing Information (USPI) of ketamine HCl for injection states that an IV injection of 2 mg/kg can induce anesthesia starting within 30 seconds and lasting for 5 to 10 minutes. The Summary of Product Characteristics (SmPC) of esketamine HCl for injection states that anesthesia can be induced with 0.5 to 1 mg/kg given as a slow IV injection. Esketamine, as an anesthetic, is 2 to 5 times more potent than racemic ketamine.

---

<sup>3</sup> Mathew SJ, Shah A, Lapidus K. Ketamine for treatment-resistant unipolar depression: current evidence. *CNS Drugs*. 2012; 26:189-204.

Esketamine has a 3- to 4-fold higher affinity for the NMDA glutamate receptors than arketamine. Because of this, the Sponsor is developing esketamine and not ketamine (the racemate) for antidepressant therapy. This would also allow administration of a lower volume of medication via the IN route compared with racemic ketamine.

## 1. Chemistry

### 1.1. Drug Substance

Esketamine HCl (JNJ-54135419-AAC) chemical properties:

- Code names: s-ketamine hydrochloride, (+)-ketamine, hydrochloride, (S)-(+)-ketamine hydrochloride
- Chemical name: (2S)-2-(2-chlorophenyl)-2-(methyl amino) cyclohexanone hydrochloride
- Molecular Formula: C<sub>13</sub>H<sub>16</sub>ClNO.HCl
- Molecular Weight: 274.2 g/mol

The HCl salt of esketamine was selected by the Sponsor for development and exhibits chemical and physical stability at the conditions of use (room temperature). The hydrochloride salt is freely soluble in water at the pH range of 4.0-5.0, which is suitable for the preparation of the drug product as a nasal spray solution.

### 1.2. Drug Product

Esketamine HCl is supplied as a nasal spray solution with a concentration of 161.4 mg/mL and a base equivalent concentration of 140.0 mg/mL packaged in glass stoppered vials; and assembled with an actuator (b) (4). A vial contains a total of (b) (6) mg of esketamine HCl formulated in water and excipients [sodium hydroxide, citric acid and ethylenediaminetetraacetic acid disodium salt (EDTA)]. The nasal spray device has a fill volume of (b) (6) µL and a delivery volume of (b) (6) µL. The average measured residual volume left in the nasal spray device after actuation is ~ (b) (6) µL ((b) (6) mg base).

The stoppered vials are assembled into a manually activated IN dual spray device with a spray indicator (Sponsor's Figure 1). When actuated, the device dispenses 2 individual sprays delivering a total volume of 0.2 mL of esketamine HCl. Each 0.2 mL delivers 32.3 mg of esketamine HCl or 28.0 mg of the free base form. On the device, the indicator feature displays 2 colored dots, with a clear dot indicating that the device has been actuated. The indicator thus allows for differentiation between used and unused devices. The medication will be supplied in a limited pack size containing 1, 2, or 3 devices to deliver the prescribed dose of 28, 56, or 84 mg, respectively.

According to the Sponsor, the device's actuator (b) (4) features, and needs at least (b) (4) of force to pull the device apart, making it difficult to disassemble. However, there were no studies or original data submitted under the NDA to substantiate this claim.

**Figure 1: Intranasal Dual Spray Device and Spray Indicator**



Esketamine will be administered intranasally at 56 or 84 mg (base) once or twice a week, or every other week, under the observation and direction of a health care professional. The 56-mg dose is administered using 2 devices (4 individual sprays) and the 84-mg dose is administered using 3 devices (6 individual sprays). The dosing regimen proposed is delivered in two phases, an induction phase for weeks 1 - 4, at a starting dose of 56 mg of esketamine, and a maintenance phase for week 5 (b) (4) administered as either 56 or 84 mg of esketamine. The Sponsor then recommends assessing the patient's need for continued treatment, as detailed in the Sponsor's Table 1. (b) (4)

**Table 1: Recommended Dosing of Esketamine in TRD Patients**

Induction Phase	Maintenance Phase
Weeks 1-4 (two treatment sessions <sup>a</sup> /week): Starting Day 1 dose <sup>b</sup> : 56 mg Subsequent doses: 56 mg or 84 mg	Weeks 5-8: 56 mg or 84 mg once weekly From Week 9: 56 mg or 84 mg every 2 weeks or once weekly <sup>c</sup>
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment	(b) (4)

(b) (4)

<sup>c</sup> Dosing frequency should be individualized to the lowest frequency to maintain remission/response.

## 2. Nonclinical Pharmacology

### 2.1. Receptor Binding and Functional Assays

Esketamine and arketamine, the enantiomers of ketamine, and ketamine and the primary metabolite for each drug were evaluated as NMDA receptor (NMDAR) antagonists using [<sup>3</sup>H]MK-801 binding as an assay for determining antagonist binding affinities (Edert et al., 1997). Esketamine, arketamine and

ketamine, where shown to be selective for NMDAR (the PCP site of the NMDA receptor) at  $K_i$ -values in the micromolar range, 0.3, 1.4, and 0.53  $\mu\text{M}$ , respectively (Edert et al., 1997). The primary active metabolites, S-Norketamine (noresketamine), R.-Norketamine and norketamine also bound to NMDAR with  $K_i$ -values in the micromolar range, 1.7, 13, and 3.6  $\mu\text{M}$  (Edert et al., 1997). Each of the substances, including esketamine, produces antagonistic activity by blocking the cation channel of the receptor noncompetitively, without co-occupancy by glutamate. However, esketamine has greater potency in its NMDAR antagonist activity than ketamine and arketamine. Based on assessments conducted by the Sponsor, the affinity of esketamine for NMDARs is approximately 1.5- to 2.8-fold higher than that of ketamine and 4-fold higher than that of arketamine.

The Sponsor also evaluated esketamine, noresketamine, ketamine, and arketamine in several receptor screenings for off-target receptor binding (at 10  $\mu\text{M}$  concentrations; testing approximately 52 receptors) using human recombinant (CHO and HEK-293) and rat cerebral cortex samples. The data revealed esketamine activity of >50% binding inhibition at the opiate- $\mu$ , and - $\kappa$  receptors (Report 100006490), while there was no significant binding shown at any target for the esketamine metabolite noresketamine, and the counterpart substances ketamine and arketamine (Report 100006490, 100002086, 00030088\_FK12075). In follow-up cellular functional assays conducted by the Sponsor to measure for esketamine induce opiate- $\mu$ , and - $\kappa$  activity, no opiate agonist or antagonist effect by esketamine and its metabolite noresketamine was observed up to a concentration of 10  $\mu\text{M}$ . The same was found with ketamine and arketamine (Report 100030089\_FK12073).

Functionally, ketamine is well known to enhance monoaminergic neurotransmission via blockage of DAT, SERT and NET; the same is reported for esketamine at these transporters (Hancock et al, 1999, Nishimura et al 1999, Smith, et al 1981). The DAT, SERT, and NET  $K_i$  values reported for ketamine (66.8, 182, 62.9  $\mu\text{M}$ , respectively) and esketamine (46.9, 156, 64.8  $\mu\text{M}$ , respectively) are similar, while the binding affinity of arketamine is less (390, 184, 68.9  $\mu\text{M}$ , respectively) (using [ $^3\text{H}$ ]DA, [ $^3\text{H}$ ]5-HT, [ $^3\text{H}$ ]NE uptake in HEK293 cells expressing rat DAT, SERT or NET, Nishimura et al., 1999). When considering the plasma levels of esketamine in humans, plasma and estimated brain levels of esketamine are about 1  $\mu\text{M}$ , and the therapeutic dose of 84 mg on average has a  $C_{\text{max}}$  of 95 to 164 ng/mL and this equals to 0.4 to 0.7  $\mu\text{M}$ , levels that are far lower than the  $\text{IC}_{50}$  and  $K_i$  values that are reported in the above mentioned studies. Thus, the estimated receptor binding potencies for esketamine greatly exceeding 1  $\mu\text{M}$  are probably not relevant to explain the pharmacological properties of IN esketamine at the dose levels recommended for TRD and supratherapeutic doses of the drug.

Results show that esketamine, ketamine and arketamine have a similar pharmacological binding profile. For ketamine and esketamine, binding data supports the notion that esketamine is likely similar to ketamine in abuse potential.

## 2.2. Findings from Safety Pharmacology and Toxicology Studies

The following sections include a review of the toxicological studies conducted by the Sponsor that evaluated the general neurobehavioral effects of esketamine when tested in single-dose and repeated-

dose studies. Additional toxicokinetic studies were conducted with esketamine (and ketamine) but are not discussed in this review<sup>4</sup>.

### Esketamine Toxicity

Esketamine administered intranasally was evaluated in 1 single dose toxicity study carried out with male dogs, and in 5 repeat-dose toxicity studies, 3 with male and female rats (Sprague-Dawley), and 2 with male and female dogs (Beagle). Also, there were 8 neurotoxicity studies examining adult and juvenile rats (Sprague-Dawley) administered esketamine (and ketamine), which included 6 studies with female rats and two studies with male and female rats.

In animal toxicity studies, esketamine produced multiple neurobehavioral effects:

#### *Single-dose studies*

Dog- Report TOX13114: licking, ataxia, head shaking, excitation decreased, and general activity, (28, 65 mg IN, 28 mg IV, and 28 mg given by oral gavage)

#### *Repeated-dose studies*

Dog- Report TOX10524 (with Recovery period): increased or decreased general activity, ataxia, and head shaking (12, 24, and 36 mg IN).

Dog- Report TOX10701: short-lasting incoordination, and increased activity; neurological examinations showed no treatment-related findings (12, 24, and 36 mg IN).

Rats- Report TOX12233<sup>5</sup>: ataxia, decreased general activity, excitation and catalepsy (20, 40, 80, and 160 OP)

Rats -Report TOX10517: increased general activity, ataxia; 1-month recovery period of which all rats fully recovered, no esketamine-related effects were observed [0.9, 3, and 9 mg IN (equivalent to approximately 2.7, 9, and 27 mg/kg in rats weighing 300 g)]

Rats - Report TOX10768: functional observational battery (FOB) results of esketamine-related unsteady gait, underactive behavior, overactive behavior, slow and/or poorly coordinated righting, reflex, abnormal gait, increased landing foot splay and reduced grip strength, and increased cage floor activity; Morris Maze results of esketamine-related no evidence of an adverse effect of esketamine HCl administration on learning and memory ability; locomotor activity test was unaffected by esketamine [0.9, 3, and 9 mg IN (equivalent to approximately 2.7, 9, and 27 mg/kg in rats weighing 300 g)]

---

<sup>4</sup> The Sponsor conducted in vitro and in vivo genotoxicity, carcinogenicity, reproductive and developmental toxicity, impurity, and neurotoxicity studies with esketamine and ketamine and included a published literature review on the embryo-fetal neurotoxicity potential of ketamine. These studies were not evaluated in this review.

<sup>5</sup> Report TOX12233, was an up to 14-day single- and repeated-dose toxicity study.

The behavioral effects reported in Report TOX10768 were dose-dependent, occurring mainly at 3 and 9 mg of esketamine. Systemic exposure levels of esketamine was generally similar in male and female rats, with the exception of Day 1 Cmax and AUC0-t at 3 mg being higher in females than males but lower for females at 0.9 mg at week 26. Systemic exposure of rats to the metabolite noresketamine increased with an increased dose of esketamine. However, increases (AUC0-t) were proportionally lower in males than females over the dose range (0.9 – 9.0 mg/day0).

### **2.3. Animal Behavioral Studies**

The preclinical behavioral studies pertaining to the abuse potential, tolerance and physical dependence of esketamine were described using published literature data evaluating ketamine. Since esketamine is an enantiomer of ketamine, findings reported with ketamine should be considered as evidence of the potential effects with esketamine.

The psychotomimetic properties of ketamine are mainly thought to be caused by the S-enantiomer, otherwise known as esketamine (Vollenweider et al., 1997; Engelhardt, 1997). Much like esketamine, ketamine binds to the PCP-binding site of the NMDAR complex, located within the ion channel, which results in opening of the ion channel and neuronal depolarization.

Ketamine has been shown to function as a reinforcer when tested in a self-administration paradigm (rhesus monkeys: Moreton et al., 1977, Carroll et al, 1983, Broadbear et al., 2004; baboons: Lukas et al., 1984; rat: O'Connor et al., 2011) as well as to generalize to PCP when tested in a drug discrimination paradigm (Poling et al., 1979; Holtzman et al. 1980; Shannon, 1981; Young et al., 1981).

Rhesus monkeys with a previous history of IV cocaine self-administration, self-administered ketamine during daily 2-hour sessions and did so over a wide range at fixed-ratio schedules of reinforcement (1, 8, and 64) producing an inverted U-shaped curve (Moreton et al., 1977). For drug discrimination, in rats, ketamine showed approximately 1/10<sup>th</sup> the potency of PCP in producing PCP-like discriminative stimuli and had a more rapid onset of action (Shannon, 1981).

While there were no self-administration or drug discrimination studies found for esketamine in the published literature at the time of this review, the condition place preference of esketamine has been evaluated (Yang et al, 2015). The study was conducted in mice. There were no relevant differences found between esketamine and ketamine. Esketamine (5, 10, and 20 mg/kg IP) and ketamine (10 mg/kg IP) significantly increased conditioned place preference scores, while arketamine (5, 10, and 20 mg/kg IP) had no effect. The data suggests that esketamine and ketamine, but not arketamine, may induce rewarding effects. Also, results show that esketamine is most similar to ketamine.

### **2.4. Tolerance and Physical Dependence Studies in Animals**

Several nonclinical studies have demonstrated tolerance to the effects of ketamine (White and Ryan, 1996). In addition, its potential for dependence and withdrawal has been shown in animals (Beardsley and Balster, 1987, Walgren et al., 2014). Rats and monkeys demonstrated withdrawal effects, including

significant decreases in operant responding, when ketamine was no longer given (Beardsley and Balster, 1987), as well as increased reactivity, increased activity, and stereotypic behaviors. In male monkeys, BID oral administration of 150 mg/kg ketamine produced observable effects of decreased activity, loss of balance, ataxia, hunched posture, nystagmus, lateral recumbence, and changes in alertness levels over a 5-day dosing phase. Following repeat dosing of 150 mg/kg for 14 days, monkeys demonstrated increased reactivity, increased activity, and stereotypic behaviors when tested during subsequent withdrawal assessments when esketamine was no longer given.

Clinical symptoms of dependence and psychological withdrawal after the prolonged use of ketamine have also been reported. However, there is no adequate data to characterize a withdrawal syndrome associated with physical dependence (see Section: Tolerance and Physical Dependence Studies in Humans).

### **3. Clinical Pharmacology**

#### **3.1. Absorption, Distribution, Metabolism, Elimination (ADME)**

Esketamine's PK in plasma, following IN administration, is characterized by high clearance, a large volume of distribution and moderate absolute bioavailability in animals and in humans. The primary in vivo metabolic route was N-demethylation to the pharmacologically active (but less potent) metabolite noresketamine (other metabolites were evaluated but are not discussed in this review because they represent less than 10% of total drug plasma levels<sup>6</sup>).

There was no accumulation of the drug after repeated administration. Among the metabolites assayed, only one, noresketamine, was characterized as having some activity (3- to 5-fold lower than the parent drug) and was shown to account for 12% to 14% of the total drug levels in plasma.

In humans, IN administered esketamine HCl had a median T<sub>max</sub> of 0.37 and 0.82 hours at 28 and 112 mg (C<sub>max</sub> ranging from 63.3 to 151 ng/mL) respectively, and an elimination half-life (t<sub>1/2</sub>) ranging from 5.86 to 9.83 hours. Concentrations of esketamine were collected 7 minutes after the first dose, in all IN regimens. Additionally, following IN administration of esketamine (at 28 to 112 mg) metabolite noresketamine had a median T<sub>max</sub> of 1.25 to 2.5 hours (C<sub>max</sub> ranging from 60.1 to 122 ng/mL), and an elimination half-life (t<sub>1/2</sub>) ranging from 6.68 to 8.82 hours.

It is important to note that the plasma levels of esketamine in humans treated at the maximum recommended therapeutic dose of 84 mg IN esketamine HCl are, on average, 95 to 164 ng/mL or 0.4 to 0.7 μM. As specified by the Sponsor, using rat PK parameters and plasma levels from clinical studies, the NMDAR occupancy by ketamine and norketamine is estimated to be 31% at the dose regimen used in studies with ketamine in depressed patients, i.e., IV infusion at 0.5 mg/kg for 40 minutes.

---

<sup>6</sup> Other metabolites evaluated with plasma area under the curve from 0 to 24 hours (AUC<sub>0-24h</sub>) values >25% of parent esketamine included: JNJ-64111060 (M4/2S,6S-hydroxynorketamine (2S,6S-HNK)); JNJ-64115922 (M19/1S,2S,3S)-3-amino-3-(2-chlorophenyl) cyclohexane-1,2-diol (keto-reduced M4; keto-reduced 2S,6S-HNK); JNJ-68414463 (M5/2S,5S-hydroxynorketamine (2S,5S-HNK)) and JNJ-65402454 (M9/5,6-dehydronoresketamine (2S-5,6-DHNK)).

## 4. Clinical Studies

### 4.1. Overview

The goal of the Sponsor's Phase 2 and 3 clinical studies in TRD was to assess the efficacy, safety, and tolerability of induction and maintenance treatment with esketamine. The antidepressive mechanism of action of ketamine and esketamine is distinct from conventional monoaminergic treatments and ketamine affects fast excitatory glutamate transmission, increases brain-derived neurotrophic factor (BDNF) release, and stimulates synaptogenesis.

In the Phase 2 TRD studies, esketamine (or placebo nasal spray) was given adjunctively with the ongoing antidepressant (AD) treatment(s) being administered at the time of study entry. In all Phase 3 studies, esketamine (or placebo nasal spray) treatment was given in addition to an oral AD therapy that was started at the beginning of the induction phase (i.e., newly initiated). Therefore, the control group in the Phase 2 studies, consisting of placebo nasal spray, is referred to as placebo, while the comparator group in the Phase 3 studies, consisting of an oral AD plus placebo nasal spray, is referred to as oral AD plus placebo to remind the reviewer that the comparator treatment was active.

The results of Phase 2 double-blind (DB), placebo-controlled studies demonstrated a rapid onset and significant antidepressant effect for esketamine. Twice-weekly esketamine significantly improved depressive symptoms in adults with TRD. Efficacy was dose-related, with doses of 56 mg and 84 mg demonstrating significantly greater efficacy than placebo. The 28 mg dose had a shorter duration of response, and the 14 mg dose was ineffective. The clinical effect was observed as early as 2 hours after the first dose. In the open-label (OL) phase (Days 15-74) following the DB period, in which the frequency of esketamine dosing was reduced to once weekly for 2 weeks and then to every 2 weeks, the antidepressant response appeared to persist for approximately 2 months after the last dose of esketamine.

The primary safety assessment was based on the 6 completed Phase 2 and 3 studies in subjects with TRD. Overall, approximately 2,283 subjects were exposed to esketamine nasal spray across the completed Phase 1 (including the HAP study), 2, and 3 studies in this application of which included 540 subjects in the completed Phase 1 studies along with 1,708 subjects in the completed Phase 2 and 3 studies in TRD.

All Phase 3 studies enrolled subjects who had moderate to severe depression and had not responded to 2 or more different oral AD treatments for the current depressive episode. In each Phase 3 study esketamine was dosed intermittently (twice weekly for induction therapy, with dosing subsequently reduced in frequency to once weekly or once every 2 weeks based on efficacy in the longer-term studies) and was given concurrently with a newly-initiated oral AD, which was dosed daily to the maximally tolerated dose. The primary efficacy endpoint in the Phase 3 studies was based on the change in depressive symptoms, as evaluated using the clinician rated Montgomery-Asberg Depression Rating Scale (MADRS). The primary endpoint in the TRD3003 relapse prevention study was time to relapse.

## 4.2. Human Abuse Potential Study

The Sponsor conducted one human abuse potential study to assess the abuse potential, safety, and tolerability of two doses of esketamine, 84 mg (maximum recommended therapeutic dose) and 112 mg, administered intranasally (IN) relative to a dose of intravenous (IV) racemic ketamine (0.5 mg/kg/40 minutes).

The next sections provide a summary of the methodology and study findings.

### 4.2.1. Overview

Study TRD1015, a single center, single dose, double blind, double dummy, placebo controlled, randomized, crossover study, evaluated the abuse potential of intranasal esketamine (84 mg and 112 mg) compared to racemic intravenous ketamine (0.5 mg/kg/40 minute), in 34 nondependent healthy volunteers (subjects). The volunteers were current polydrug recreational users, who had used at least two types of perception-altering drugs within 3 months prior to the study and reported use of racemic ketamine at least once in their lifetime, without perceived moderate or severe adverse effects.

The study was conducted at a single site [REDACTED] (b) (4) Subjects did not remain at the study center for the duration of the study and were discharged in between treatments.

### 4.2.2. Objectives

*Primary Objective:* To evaluate the abuse potential of esketamine in nondependent, recreational polydrug users of perception-altering drugs.

*Secondary Objectives:*

To evaluate

- The relationship between select measures of abuse potential and the dose of intranasal (IN) esketamine.
- To assess the safety and tolerability of IN administered esketamine and intravenous (IV) racemic ketamine, and
- To measure the pharmacokinetics (PK) of IN esketamine and IV racemic ketamine.

### 4.2.3. Study drug, dose selection and dose administration

Racemic ketamine (50:50 percent (*S*)-ketamine and (*R*)-ketamine) was used as the positive control, and administered as an injectable solution of ketamine hydrochloride, containing 10 mg/mL of ketamine base. The solution was diluted with saline to administer an IV dose of 0.5 mg/kg in 40 minutes. (Note; Racemic ketamine will be referred from this point on in this review as ketamine).

Ketamine IV is used in anesthesia at doses that may range from 1 mg/kg to 4.5 mg/kg, and in adult patients a dose of 1 mg to 2 mg/kg administered at a rate of 0.5 mg/kg/min is used for induction (Ketalar label). The Sponsor selected a dose of ketamine of 0.5 mg/kg administered over 40 minutes. This dose has also been studied by others to evaluate the subjective effects of intravenous ketamine (Krystal et al., 1994; Bowdle et al., 1998). Krystal et al. also used a 40-minute infusion time. Bowdle et al. reported a linear relationship between the ketamine subjective effects and plasma concentrations between 50-200 ng/mL. This exposure is expected with the ketamine IV infusion of 0.5 mg/kg over 40 minutes, which is shown to achieve a mean plasma ketamine C<sub>max</sub> of about 200 ng/mL in patients with TRD. This C<sub>max</sub> is lower than the dose range typically associated with waking from anesthesia induced by ketamine (500-1000 ng/mL)(Domino, 2010).

Esketamine was administered using a nasal spray pump unit. The spray unit delivered 16.14 mg of esketamine HCl (14 mg esketamine base) solution per a 100 µL spray, and delivered 2 sprays per unit. Thus, an 84 mg dose would be delivered in 6 sprays and the 112 mg dose in 8 sprays. The sprayed solution consisted of (b) (4) mg/mL of esketamine HCl (equivalent to (b) (4) mg of esketamine base) in (b) (4) mg/mL ethylenediaminetetraacetic acid (EDTA) and (b) (4) mg/mL citric acid in water for injection with a pH of 4.5.

The doses of IN esketamine included in this HAP study were 84 mg and 112 mg. The highest IN esketamine dose included in the Phase 2 and 3 studies was 84 mg. Based on reports of euphoria and effects on perception reported in the clinical studies with esketamine, it was expected that drug-liking would be observed at the IN esketamine dose of 84 mg. A suprathreshold dose of IN esketamine was tested to potentially provide dose-related differentiation of PD responses. An esketamine dose greater than 112 mg was not tested, given the concern that perceptual and sedative effects associated with higher doses of esketamine could prevent the subjects from completing the PD assessments.

The placebo spray consisted of water for injection to which a (b) (4) at a concentration of (b) (4) mg/mL was added to mask the taste of the IN esketamine. Placebo was provided in matching esketamine nasal spray pump devices (Study TRD1015, Protocol amendment)

#### 4.2.4. Study design

Study TRD1015 was a single-center, single-dose, double-blind, double-dummy, placebo-controlled, randomized crossover study.

The study consisted of a Screening Visit (SV) and two double-blind phases, a Qualification Session (QS) and a Treatment Phase. The Screening Visit determined eligibility for participation based on the inclusion and exclusion criteria.

On Day 1 of the QS, subjects who still met the enrollment criteria were randomized to receive IV control, IN test drug or matching IV or IN placebo. On Day 1 of the QS, subjects also completed a practice session to train and prepare for pharmacodynamic testing. On Day 1, 2, and 3 of the QS, in addition to receiving study drug, subjects participated in serial PD assessments of abuse potential to assess eligibility for the TP. On Day 3 of the QS, after completion of the final PD assessments, all subjects were discharged from the study center. Subjects remained at the study center at least 10 hours before drug administration and until completing all assessments given on Day 3 of the QS, and if

participating in the TP subjects remained until completing all measures and safety assessments after receiving each treatment.

Subjects were eligible to continue into the TP if they were able to complete the study-related procedures, and could tolerate the IV ketamine dose and IN placebo, along with demonstrating a  $\geq 15$  point difference, relative to placebo, in maximum response (E<sub>max</sub>) on Drug Liking at the Moment within the first 4 hours after administration of 0.5 mg/kg of IV ketamine over 40 minutes. Subjects also needed an acceptable placebo response, defined as  $\geq 40$  and  $\leq 60$  points for Drug Liking at the Moment during the 4 hours after administration of placebo.

The TP was a randomized, single-dose, double-blind, double-dummy, placebo-controlled phase in which 4 treatments (IV placebo/IN placebo, 0.5 mg/kg IV ketamine/IN placebo, IV placebo, IV placebo/IN 84 mg esketamine, or IV placebo/IN 112 esketamine) were administered in a cross-over manner to measure the likelihood of abuse. On Day 1 of the first period, subjects were randomly assigned to 1 of 4 treatment sequence groups. Each of the 4 treatments to be administered on Day 1 in the TP consisted of an IV dose administered concurrently with an IN dose of study medication. All study drug administrations were double blind and took place between 7:00 am and 10:00 am and at approximately the same time ( $\pm 1$  hour) for a given subject on Day 1 of each period.

There was a 7-14 day window between drug administration on Day 2 of the QS and Day 1 of the first period of the TS.

Subjects did not remain at the study site for the length of the study. Subjects, who met inclusion/exclusion criteria, were readmitted to the study center on Day 1 of each of the 4 periods of the TP. On Day 1 of each treatment in the QS and TP, subjects received a urine drug test and alcohol breath test

#### *4.2.5. Eligibility and number of subjects*

Full inclusion and exclusion criteria can be found in the Sponsor's Study TRD 1015 Protocol Amendment. Subjects enrolled included men and women, 18 to 55 years old (inclusive), with a body mass index (BMI) between 18 to 30 kg/m<sup>2</sup>, and a body weight not less than 50 kg. As per the inclusion criteria regarding current drug use, the subjects needed to be current, polydrug recreational users who were nondependent, nonmedical users of at least 2 types of perception-altering drugs of abuse [e.g. lysergic acid diethylamide (LSD), cannabinoids, ketamine, ecstasy/3,4-methylenedioxy-methamphetamine, PCP, psilocybin, and ring-substituted amphetamines with perception altering effects] including at least 10 total lifetime occasions of use and were reported to like the drug's effects.

A total of 55 subjects participated in the QS, of these 55 subjects, 41 completed the QS. Fourteen subjects were discontinued, 12 subjects did not meet all predefined criteria, and 2 subjects were discontinued for reasons coded as "Other" (1 subject received corresponding dose outside the pre-specified dosing window, and the other did not complete treatment on Day 1 within the specified protocol window).

Forty-one subjects participated in the TP. However, only 34 completed the study. Seven subjects were discontinued from the study.

- One subject (Subject (b) (6)) experienced an increase in transaminases (alanine aminotransferase and aspartate aminotransferase) during Day 1 of the Treatment Period 2. This subject had received IN placebo/IV placebo (Treatment A) in Period 1 and supposed to had received IV placebo/112 mg esketamine (Treatment D). The Sponsor reports that the event was considered mild and resolved at the end of the study.
- One subject (Subject (b) (6)) was withdrawn after completing Period 2 (IV placebo/IN placebo, Treatment A) due to a positive urine drug screening, positive for cocaine and benzodiazepines. This subject received 0.5 mg/kg IV ketamine/IN placebo (Treatment B) in Period 1.
- One subject was discontinued (Subject (b) (6)) after completing Period 1 (0.5 mg ketamine/IN placebo, Treatment B) due to being dosed outside of protocol specified dosing window in Period 2 (IV placebo/IN placebo, Treatment A)
- Two subjects (Subject (b) (6)) were discontinued after completing Period 3 (Treatment A, IV placebo/IN placebo) based on the clinical judgement of the physician at the study site. Both subject had received IV placebo/ IN 112 mg esketamine (Treatment D) in Period 1, and IV placebo/IN 84 mg esketamine (Treatment C) in Period 2.
- One subject (Subject (b) (6)) was withdrawn from the study after completion of Period 2 (IV placebo/IN 112mg esketamine, Treatment D) based on the discretion of the principal investigator. This subject had received IV placebo/IN placebo (Treatment A) in Period 1.
- One subject (Subject (b) (6)) was withdrawn from the study after completion of Period 1 (0.5 mg/kg IV ketamine/IN placebo, Treatment A) based on the discretion of the principal investigator.

The mean (SD) age of subjects in the TP was 26.8 (5.97) years. There were more male subjects (N=26, 63.4%) compared to female subjects (N=15, 36.6%). The mean (SD) baseline BMI was 22.72 (2.491) kg/m<sup>2</sup>. The majority of the subjects were white (35 subjects, 85.4%), 2 subjects (4.9%) were Black or African American, and 1 subject (2.4%) was Asian.

#### 4.2.6. Pharmacokinetic sampling and findings

Pharmacokinetic sampling started on Day 1 of the TP and for a period up to 24 hours postdose during each period of the TP. Samples were taken at predose, at 10 minutes and in a 10 minutes-interval for the first 40 minutes, at 1 hour and every half hour for the first 4 hours, at 8 h and 12 hours postdose. Blood samples were collected for determination of plasma concentrations of racemic ketamine, esketamine, and corresponding metabolites (racemic norketamine and noresketamine). The 40-minute sample was to be collected just prior to the end of the IV infusion.

Full PK profiles of ketamine and norketamine were available for 37 subjects who received ketamine IV, and full PK profiles of esketamine and noresketamine were available for 36 subjects who received the lower dose of esketamine (IN 84 mg) and for 37 subjects who received the highest dose of esketamine (IN 112 mg) tested.

*PK of Ketamine:* After administration of a single IV infusion of 0.5 mg/kg ketamine over a duration of 40 minutes, mean C<sub>max</sub> was 206 ng/mL and was observed around the time of the end of infusion with a median T<sub>max</sub> of 0.63 hours, as presented in **Table 2**, which has been reproduced from the Final Study Report provided by the Sponsor (Table 10, Page 55, Study Report TR1015). The mean AUC<sub>last</sub> and AUC<sub>∞</sub> values were 439 ng.h/mL and 451 ng.h/mL, respectively. The mean apparent terminal elimination half-life of ketamine was 6.1 hours.

For *norketamine* the mean C<sub>max</sub> was 98.7 ng/mL with a median T<sub>max</sub> of 0.97 hours with individual values ranging from 0.97 to 2.97 hours. Mean AUC last and AUC<sub>∞</sub> values were 697 mg.h/mL and 764 ng.h/mL, respectively; and a mean apparent terminal half-life of 7.7 hours.

**Table 2:** Pharmacokinetic Parameters of Ketamine and Norketamine after IV Administration of Ketamine at 0.5 mg/kg with Intranasal Placebo (Reproduced from Study Report TRD1015, page 55 and page 57)

Pharmacokinetics of ketamine	Ketamine 0.5 mg/kg IV	Norketamine after Ketamine 0.5 mg/kg IV
	Mean (SD); T <sub>max</sub> , Median (range)	
<b>N</b>	37 <sup>a</sup>	37 <sup>a</sup>
<b>C<sub>max</sub> (ng/mL)</b>	206 (59.9)	98.7 (28.0)
<b>T<sub>max</sub> (hour)</b>	0.63 (0.52-0.73)	0.97 (0.97-2.97)
<b>AUC<sub>last</sub> (ng.h/mL)</b>	439 (67.3)	697 (196)
<b>AUC<sub>∞</sub> (ng.h/mL)</b>	451 (75.0)	764 (229)
<b>t<sub>1/2</sub> (h)</b>	6.1 (1.7)	7.7 (2.2)

<sup>a</sup>. N=31 for AUC<sub>∞</sub>, and t<sub>1/2</sub>; **h = hour**

As seen in **Table 2** above C<sub>max</sub> values for norketamine are lower than for ketamine, whereas exposure was higher (higher AUC).

*PK of Esketamine:* After the administration of a single IN dose of 84 or 112 mg esketamine, the mean esketamine C<sub>max</sub> for each dose was 128 and 159 ng/mL, respectively, as seen in **Table 3**. The data included in **Table 3** have been extrapolated from the final Study Report TRD1015 (See Table 10, 11, 12 and 13, pages 55-61, Study Report TRD1015). The mean AUC<sub>last</sub> and AUC<sub>∞</sub> values were 386 ng.h/mL and 389 ng.h/mL, respectively, and 514 ng.h/mL and 559 ng.h/mL, respectively, after dosing with 84 mg and 112 mg esketamine, respectively. Also, following 84 and 112 mg esketamine, the median T<sub>max</sub> was similar at 0.63 hours and 0.65 hours, respectively and the mean apparent terminal elimination half-life was similar at 6.6 and 6.9 hours, respectively.

For *noresketamine*, after a single 84 mg or 112 mg IN dose of esketamine, mean C<sub>max</sub> values were 290 and 353 ng/mL respectively, and with a median T<sub>max</sub> of 1.48 hours (range 0.97-2.97 hours) and 1.97 (range 0.97 to 3.97 hours) after IN administration of 84 mg and 112 mg respectively. The mean noresketamine AUC<sub>last</sub> and AUC<sub>∞</sub> were 1534 ng.h/mL and 1,637 ng.h/mL respectively and after administration of 84 mg IN esketamine. After administration of IN 112 mg, the mean noresketamine

mean  $AUC_{last}$  and  $AUC_{\infty}$  were 2019 ng.h/mL and 2,202 ng.h/mL, respectively. The apparent terminal half-life was similar for both doses and averaged 6.7 hours.

**Table 3:** Pharmacokinetic Parameters of Esketamine and Noresketamine after IN Administration of Esketamine 84 mg or 112 mg (Reproduced from Study Report TRD1015, page 59 and page 61)

Pharmacokinetics of esketamine	IN Esketamine 84 mg	Noresketamine after IN Esketamine 84 mg	IN Esketamine 112 mg	Noresketamine after IN Esketamine 112 mg
	Mean (SD); Tmax, Median (range)			
<b>N</b>	36 <sup>a</sup>	36 <sup>a</sup>	37 <sup>b</sup>	37 <sup>b</sup>
<b>C<sub>max</sub> (ng/mL)</b>	128 (49.5)	290 (116)	159 (51.3)	353 (118)
<b>T<sub>max</sub> (hour)</b>	0.63 (0.13-1.97)	1.48 (0.97-2.97)	0.65 (0.30-2.97)	1.97 (0.97-3.97)
<b>AUC<sub>last</sub> (ng.h/mL)</b>	386 (90.6)	1534 (541)	514 (1266)	2019 (691)
<b>AUC<sub>∞</sub> (ng.h/mL)</b>	389 (94.6)	1637 (608)	559 (134)	2202 (804)
<b>t<sub>1/2</sub> (h)</b>	6.6 (1.7)	6.7 (1.6)	6.9 (2.1)	6.7 (1.5)

<sup>a</sup>. N=31 for  $AUC_{\infty}$ , and  $t_{1/2}$

<sup>b</sup>. N=32 for  $AUC_{\infty}$ , and  $t_{1/2}$ ; **h = hour**

#### 4.2.7. Abuse potential endpoints- pharmacodynamics

Several pharmacodynamic measures were performed to capture the subjective effects of IV ketamine and IN esketamine using a series of bipolar and unipolar visual analog scales (VAS) as detailed in **Table 4**.

The study primary endpoint was the VAS Drug Liking at the Moment (bipolar). Although, the exact question presented to subjects was not explicitly stated in the Study Report, in general subjects are asked, if they “like the drug effect they are feeling at the moment,” and a score of 0 indicates strong disliking; values of 50 indicate neither like or dislike; and values of 100 indicate strong liking.

**Table 4:** Pharmacodynamic Tests Performed

VAS for Balancing Measures	Positive Effects at the Moment	Negative Effects at the Moment	Perceptual Effects	Others
Drug Liking at the Moment (bipolar)	VAS for High (unipolar)	VAS for Bad (unipolar)	VAS for Hallucinating (unipolar)	VAS for Dizziness (unipolar)
Overall Drug Liking (bipolar)	VAS for Good (unipolar)	VAS for Nausea (unipolar)	VAS for Floating (unipolar)	VAS for Any Effects (unipolar)
Take Drug Again (bipolar)			VAS for Detached (unipolar)	VAS for Sedation (unipolar)
			VAS for Spaced Out (unipolar)	Drug Similarity
			VAS for Vision Clear, Crisp (bipolar)	

A total of 55 subjects participated in the QS, of the 55 subjects, 41 subjects completed the QS and 14 subjects were withdrawn: 12 subjects did not meet all pre-defined criteria and 2 subjects were withdrawn due to “Other” reasons (1 subject was dosed outside of the protocol specified dosing window and the other subject was unable to complete Treatment 1 within the protocol defined window).

All scales were administered at 20 minutes, 40 minutes, 1 hour, 1 hour- 30 minutes, 2 hours, 2 hours- 30 minutes, 3 hours, 4 hours, 8 hours, 12 hours, and 24 hours after dose administration. Predose measures were taken for High, Hallucination, Floating, Detached, and Spaced Out. For Drug Liking at the Moment, High and Good, scales were also administered at 10 minutes.

#### 4.2.8. Data Analysis

This section summarizes findings from the review performed by the Division of Biometrics VI, Office of Biostatistics (DARRTS, NDA 211243, Dang, Qianyu, dated 2/12/2019).

The following section provide a descriptive statistical analysis and statistical testing for the primary endpoint (Drug Liking at the Moment) and secondary endpoints (Take drug Again, Overall Drug Liking, Hallucinating, Floating, Detached and Space out)

#### 4.2.9. Descriptive statistical analysis

The primary endpoint of Drug Liking at the Moment and secondary endpoints of Take Drug Again and Overall drug liking were assessed by administering a 100-point bipolar VAS. Perceptual effects for Hallucinating, Floating Detached and Spaced Out were measured by using a unipolar scale where minimum values were 0 and higher values 100.

**Table 5** summarizes mean values, standard deviation (SD), minimum scores, first quartile scores (Q1), median values (Med), third quartile scores (Q3) and maximum (Max) for study treatments, and for primary and analyzed secondary endpoints.

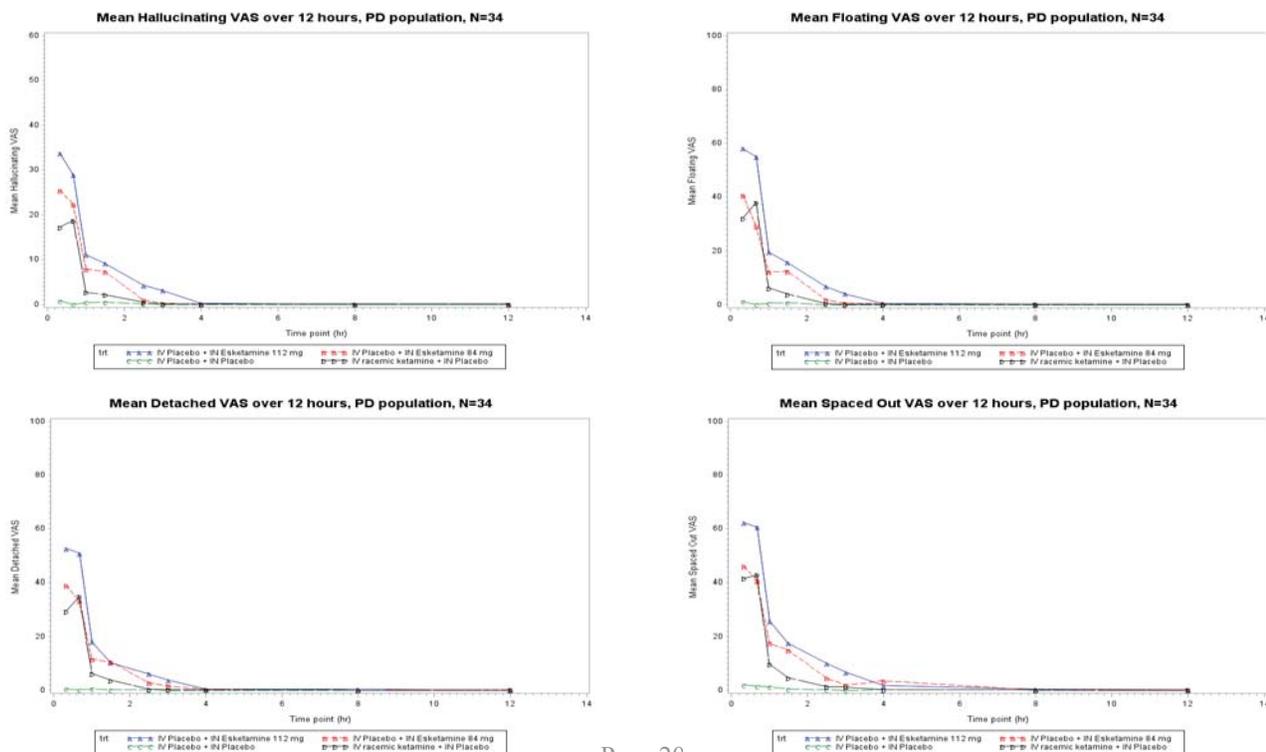
**Table 5:** Summary Statistics for Primary and Secondary Emax Endpoints (Source: DARRTS, NDA 211243, Dang, Qianyu, dated 2/12/2019)

	Treatment	Mean	SD	Min	Q1	Med	Q3	Max
Drug Liking (Bipolar) Emax (N=34)	Esketamine 112mg	83.7	15.0	50	72	88	95	100
	Esketamine 84 mg	82.7	13.0	54	75	82	94	100
	Ketamine	83.6	15.5	50	72	86	100	100
	Placebo	50.4	1.1	50	50	50	50	56
Take Drug Again (hour 8) (Bipolar) Emax (N=34)	Esketamine 112mg	76.6	19.9	32	63	77	98	100
	Esketamine 84 mg	77.1	18.5	46	60	83.5	92	100
	Ketamine	76.9	17.7	48	60	75	93	100
	Placebo	50.8	10.0	29	50	50	50	100
Overall Drug Liking (hour 8) (Bipolar) Emax (N=34)	Esketamine 112mg	74.3	20.7	8	61	78	91	100
	Esketamine 84 mg	74.9	17.2	49	56	78.5	88	100
	Ketamine	75.2	17.3	50	61	76.5	91	100
	Placebo	51.4	8.1	36	50	50	50	92

Hallucinating (Unipolar) Emax (N=34)	Esketamine 112mg	43.3	37.6	0	2	44	73	100
	Esketamine 84 mg	31.1	34.9	0	0	12.5	64	100
	Ketamine	22.5	29.9	0	0	6.5	40	100
	Placebo	0.79	3.4	0	0	0	0	19
Floating (Unipolar) Emax (N=34)	Esketamine 112mg	69.4	30.2	0	46	73	100	100
	Esketamine 84 mg	47.8	47.8	0	18	46	77	100
	Ketamine	43.9	43.9	0	15	43	63	100
	Placebo	1.2	5.2	0	0	0	0	30
Detached (Unipolar) Emax=34	Esketamine 112mg	63.3	30.2	0	39	67	97	100
	Esketamine 84 mg	47.7	31.2	0	22	44.5	75	100
	Ketamine	41.1	31.3	0	17	36	67	100
	Placebo	0.65	2.5	0	0	0	0	14
Spaced Out (Unipolar) Emax (N=34)	Esketamine 112mg	70.9	28.4	0	52	75.5	99	100
	Esketamine 84 mg	56.5	28.1	9	35	51.5	72	100
	Ketamine	49.3	30.5	0	26	50	71	100
	Placebo	1.9	9.6	0	0	0	0	56

As summarized in **Table 5**, the means for maximum Drug Liking, Take Drug Again, and Overall Drug Liking for IN esketamine 84 mg, IN esketamine 112, and IV ketamine were similar. For perceptual effects of Hallucinating, Floating, Detached and Spaced Out, there was no difference in the means for IN esketamine 84 mg, and IV ketamine. However, the administration of IN esketamine 112 mg was associated with higher mean scores than those of IN esketamine 84 mg and IV ketamine, and as seen in **Figure 2**, these scores differences were observed in the first hour after drug administration.

**Figure 2:** Mean Time Course 12 Hours Profiles on Hallucinating, Floating, Detached, and Spaced Out for Placebo, IV Ketamine, IN Esketamine 84 mg, and IN Esketamine 112 mg.



#### 4.2.10. Statistical testing

The next sections describe the statistical testing findings for the primary endpoint and secondary endpoints.

##### - *Statistical testing for the primary endpoint*

The statistical model used for the primary analysis was a mixed-effects model which included sequence, period and treatment as mixed effects, and subject as a random effect. The FDA statistical reviewer, unlike the Sponsor, performed the analysis based on number of subjects who completed all treatment periods and followed the statistical testing procedure described in the 2017 guidance for industry, *Assessment of Abuse potential of Drugs* (Accessed at <https://www.fda.gov/downloads/drugs/guidances/ucm198650.pdf>). Thus, to evaluate the abuse potential of IN esketamine, the following comparisons were performed for the primary endpoint, Drug Liking:

1. IV racemic ketamine versus P
2. IN esketamine 112 mg versus IV ketamine
3. IN esketamine 84 mg versus IV ketamine
4. IN esketamine 112 mg versus P (only if  $H_0$  of test 2 was rejected)
5. IN esketamine 84 mg versus P (only if  $H_0$  of test 3 was rejected)

The FDA 2017 Guidance recommends the following hypotheses testing:

1.  $H_0 : \mu_C - \mu_P \leq \delta_1$  versus  $H_a : \mu_C - \mu_P > \delta_1$ ,
2.  $H_0 : \mu_C - \mu_T \leq \delta_2$  versus  $H_a : \mu_C - \mu_T > \delta_2$ , and
3.  $H_0 : \mu_T - \mu_P \geq \delta_3$  versus  $H_a : \mu_T - \mu_P < \delta_3$ ,

where  $C$ ,  $T$  and  $P$  denote IV ketamine, or IN esketamine and placebo. The Sponsor did not pre-specify  $\delta_s$ . However, the FDA's review considered the values;  $\delta_1=15$ ,  $\delta_2=0$  and  $\delta_3=11$ .

The statistical primary analysis showed that for Drug Liking:

- The study was validated as the mean scores for IV ketamine were statistically significantly greater than placebo.
- Mean Emax Drug Liking scores for both doses of IN esketamine were similar to the mean Emax scores for IV ketamine, as there was no statistical difference in means.

##### - *Statistical testing for secondary endpoints*

The statistical secondary analysis showed that for the secondary outcomes:

- For all secondary endpoints, the mean scores for IV ketamine were significantly greater than placebo ( $p < 0.001$ )

- There were no statistically significant differences in means between both doses of IN esketamine and IV ketamine for Emax Take Drug Again and Overall Drug Liking
- There were no statistically significant differences in means between IN esketamine 84 mg and IV ketamine for Emax Hallucinating, Floating, Detached and Spaced out; whereas IN esketamine 112 mg had significantly higher scores in Emax Hallucinating, Floating, Detached and Spaced out than IV ketamine.

### 4.3. Adverse Event Profile Through all Phases of Development

Adverse drug reactions (ADRs) reported by the Sponsor were adverse events (AEs) considered to be reasonably associated with the use of esketamine. The assessment of ADRs was based on data from the 6 Phase 2 and 3 studies in TRD (TRD2003, TRD3001, TRD3002, TRD3005, TRD3003, and TRD3004). A portion of the Sponsor's Table 4 (Clinical Overview, page 56): *Incidence of Treatment-Emergent ADRs Identified in Completed Phase 2 and Phase 3 Studies (Open-Label and Double-Blind Phases)* is reproduced as **Table 6**, only showing those AEs related to psychiatric disorders, nervous system disorders, general disorders and administration site conditions.

**Table 6:** Treatment Emergent Adverse Events in Completed Phase 2 and 3 Studies (Open-Label and Double-Blind Phases)

	Double-Blind Population		Open-Label	
	Esketamine + Oral AD (N=587)	Oral AD + Placebo (N=486)	Esketamine + Oral AD (N=1335)	All Esketamine Population (N=1709)
<b>Psychiatric disorders</b>	253 (43.1%)	54 (11.1%)	586 (43.9%)	788 (46.1%)
Anxiety*	63 (10.7%)	28 (5.8%)	155 (11.6%)	220 (12.9%)
Dissociation*	221 (37.6%)	30 (6.2%)	511 (38.3%)	690 (40.4%)
Euphoric mood	20 (3.4%)	3 (0.6%)	51 (3.8%)	73 (4.3%)
<b>Nervous system disorders</b>	342 (58.3%)	147 (30.2%)	830 (62.2%)	1096 (64.1%)
Dizziness*	175 (29.8%)	33 (6.8%)	490 (36.7%)	628 (36.7%)
Dysarthria*	18 (3.1%)	1 (0.2%)	37 (2.8%)	56 (3.3%)
Dysgeusia*	113 (19.3%)	54 (11.1%)	207 (15.5%)	293 (17.1%)
Headache*	115 (19.6%)	60 (12.3%)	293 (21.9%)	410 (24.0%)
Hypoaesthesia*	103 (17.5%)	7 (1.4%)	204 (15.3%)	285 (16.7%)
Lethargy*	47 (8.0%)	21 (4.3%)	95 (7.1%)	148 (8.7%)
Mental impairment	14 (2.4%)	4 (0.8%)	26 (1.9%)	41 (2.4%)
Sedation*	124 (21.1%)	35 (7.2%)	321 (24.0%)	434 (25.4%)
Tremor*	13 (2.2%)	2 (0.4%)	27 (2.0%)	45 (2.6%)
<b>General disorders and administration site Conditions</b>	45 (7.7%)	4 (0.8%)	82 (6.1%)	120 (7.0%)
Feeling abnormal	24 (4.1%)	3 (0.6%)	53 (4.0%)	72 (4.2%)
Feeling drunk	23 (3.9%)	1 (0.2%)	31 (2.3%)	51 (3.0%)

AD: antidepressant; DB: double-blind; MA: maintenance; OL: open-label; OP: optimization.

\*Represents grouped term.

Note: The following studies are included in the Double-blind Population: TRD2003 (Panels A and B DB phase), TRD3001 (DB phase), TRD3002 (DB phase), TRD3003 (MA phase), TRD3005 (DB phase). The following studies are included in the Open-label Population: TRD2003 (Panels A and B OL phase), TRD3003 (induction and OP data from direct-entry subjects), TRD3004.

Note: The 'All Esketamine Population' includes all subjects in the esketamine arm in any phase in TRD2003, TRD3001, TRD3002, TRD3003, TRD3004, TRD3005. Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. Adverse reactions are coded using MedDRA version 20.0.

There were no reported AEs of overdose or drug abuse. Approximately one-half of adult subjects treated with esketamine in the Phase 2 and 3 studies reported at least 1 AE suggestive of abuse potential, with postdose events of somnolence and dissociation being the most common. Other events, such as euphoric mood, feeling drunk, or feeling abnormal, were also observed but occurred at much lower frequencies. After up to 1 year of repeated intermittent dosing with esketamine in the Open-Label (OL) long-term safety study, the reporting frequencies of AEs of euphoric mood, feeling drunk, and feeling abnormal were 1.9% to 3.4%.

Subanesthetic doses of ketamine are known to be associated with transient, dose-related dissociation/perceptual changes. The extent of these symptoms was evaluated using the Clinician Administered Dissociative States Scale (CADSS). Dissociative/perceptual changes had an onset shortly after the start of dosing, peaked by 40 minutes postdose, and typically returned to postdose levels at the 1.5-hour postdose assessment. Over the course of each Phase 3 study, the peak mean CADSS total score at the 40-minute postdose time point in the esketamine + oral AD groups generally decreased with consecutive doses. These results indicate that the effects of esketamine are dose-dependent and that tolerance to the dissociative effects of esketamine develops.

The most common AEs of esketamine were dissociative symptoms/perceptual changes. Dissociation (grouped term) include feeling abnormal and feeling drunk. The latter 2 events were mostly reported at incidences under 5% in the Phase 2 and 3 studies and were rarely severe in intensity. However, the individual AE of dissociation was one of the most common AEs in esketamine-treated subjects across the Phase 2 and 3 studies.

Across all Phase 3 studies, reported AEs of dissociation were primarily mild or moderate in intensity, with severe events reported for <4% of subjects in each Phase 3 study. Dissociation was not considered serious for any subjects in completed Phase 2 and 3 studies and rarely led to discontinuation of study drug. In the Phase 3 studies 7 (0.4%), of the 1,601 subjects, discontinued esketamine due to an AE of dissociation. Transient dissociative/perceptual changes were more pronounced in subjects receiving the esketamine 84 mg dose than in those receiving the esketamine 56 mg doses.

Most reported AEs occurred during induction and maintenance of esketamine treatment and were reported postdose on the day of dosing and resolved the same day. Very few were assessed as severe. The AEs of dissociation and nausea appeared to be dose dependent. In each of the Phase 3 studies, most AEs were assessed by the investigator as mild or moderate in severity. Those assessed as severe were reported in 14.7% of subjects for the pooled TRD3001/TRD3002 analysis set (vs. 5.0% for total oral AD + placebo group), 4.2% for TRD3005 (vs. 1.5% for oral AD + placebo), 7.9% in DB MA phase of TRD3003 (vs. 4.1% for oral AD + placebo), and 14.7% across all study phases in TRD3004. The most frequent severe AEs (reported at the incidence of  $\geq 1\%$ ) among esketamine-treated subjects were primarily events related to the underlying disease condition (e.g., depression, anxiety) and common postdose events (e.g., dissociation, dizziness, nausea). The latter were mostly transient and resolved.

A majority of all AEs in Phase 3 studies, including those most commonly occurring in esketamine-treated subjects, were reported on the day of nasal spray dosing. Once again, AEs occurring on the day of dosing in the Phase 3 studies that were not reported as resolved on the same day consisted mainly of events considered associated with the underlying disease (e.g., depression) or with other comorbid conditions (e.g., musculoskeletal events or infections). Common postdose AEs (i.e., those consistently

reported at rates of  $\geq 10\%$  in Phase 3 studies) that were not reported as resolved the same day in  $>5\%$  of subjects were nausea and headache.

The most common severe postdose AEs that were not reported as resolved on the day of dosing in the Phase 3 studies were anxiety, insomnia, and nausea. There were no new AEs reported with long-term repeated esketamine dosing. In the Phase 3 short-term fixed-dose study TRD3001, the overall rates of AEs and serious AEs were similar for the esketamine 56 mg + oral AD and esketamine 84 mg + oral AD groups and most AEs across both dose groups were mild or moderate in severity, occurred postdose on the day of dosing, and resolved the same day. With the exceptions of dissociation and nausea (which were more common in esketamine 84 mg group), there was no conclusive evidence of a dose effect in the incidence of AEs assessed as severe with an onset on or after the second dose of nasal study drug.

The AEs leading to study discontinuation in more than 2 subjects ( $>0.1\%$ ) were (in order of frequency): anxiety, depression, blood pressure increased, dizziness, suicidal ideation, dissociation, nausea, vomiting, headache, muscular weakness, vertigo, hypertension, panic attack, and sedation. The rates of discontinuations of esketamine treatment due to AEs were generally highest immediately after treatment.

#### 4.4. Safety Profile

Safety, including targeted nasal examinations and a nasal tolerability questionnaire, were evaluated. The potential effects of study drug on dissociative symptoms were assessed using the CADSS. The Columbia Suicide Severity Rating Scale (CSSRS) was performed to assess suicidal ideation and behavior. ECGs were recorded at all sampling time points. The laboratory analysis was performed on Day 1 and Day 2 of each TP. Overall, no clinically relevant treatment-related changes in the hematology, chemistry, and urinalysis parameters were observed. During the TP, a transient increase in the mean systolic blood pressure, diastolic blood pressure, and heart rate was observed with both IV racemic ketamine and IN esketamine (84 mg and 112 mg). These transient increases returned to near baseline values 3 hours and 30 minutes postdose for each of these treatments. No clinically relevant treatment-related changes in the mean respiratory rate were observed. No AEs related to suicidal ideation/behavior were observed in this study. The nasal crusts and nasal discharge during the TP reported for most of the subjects during the QS were mild in severity. None of the subjects during the QS reported epistaxis or nasal erythema.

At least 1 safety related AE was reported in 33 (80.5%) of 41 subjects. The most frequently reported AEs ( $\geq 10\%$  of subjects) by SOCs were for psychiatric disorders (48.8% subjects), respiratory, thoracic, and mediastinal disorders (48.8% subjects), nervous system disorders (36.6% subjects), general disorders and administration site (19.5% subjects), gastrointestinal disorders (14.6% subjects), eye disorders (12.2% subjects), and infections and infestations (12.2% subjects). The most frequently reported ( $\geq 10.0\%$  of subjects) AEs were euphoric mood (31.7% subjects), nasal crusting (22.0% subjects), nasal congestion (12.2% subjects), rhinorrhea (12.2% subjects), dysgeusia (19.5% subjects), feeling abnormal (14.6% subjects), and upper respiratory tract infection (12.2% subjects).

Adverse events were classified as mild, moderate, or severe. The severe AEs were euphoric mood, dissociation, insomnia, mental status changes, nasal crusting, nasal congestion, rhinorrhea, oropharyngeal pain, dysgeusia, throat irritation, myoclonus, feeling abnormal, and hyperacusis.

#### **4.5. Evidence of Abuse, Misuse and Diversion in Clinical Trials**

There were no confirmed cases of diversion of study drug kits at any site participating in the completed Phase 3 studies, with 0.004% of all kits (4 used, 1 unused) assigned not returned to the Sponsor.

The Sponsor proposed several measures to minimize the impact of the potential for misuse, abuse, and diversion with esketamine. Some of these are included in their proposed Risk Evaluation and Mitigation Strategy (REMS). The Sponsor intends to use specialty distributors and/or specialty pharmacies to ship single-use nasal spray devices of esketamine directly to sites of care, where it will be administered under the supervision of a HCP. To help minimize the opportunity for diversion and abuse, patients will be unable to acquire esketamine nasal spray from their pharmacies.

Esketamine will be delivered through a single-use, disposable nasal spray device intentionally designed to deliver only 2 sprays of medication, to have minimal residual medication in the device after actuation, and to be difficult to disassemble. The nasal spray will be supplied in limited pack sizes containing 1, 2, or 3 devices to deliver the prescribed dose of 28, 56, or 84 mg, respectively. A program will be implemented to monitor for and report suspicious orders/sales.

#### **4.6. Physical Dependence Studies in Humans**

The terminal half-life of esketamine is 7 to 12 hours and circulating levels of esketamine do not appear to accumulate with twice-a-week or lower dosing frequency. There is no published scale that measures ketamine-specific withdrawal symptoms. The PWC-20 was developed as an instrument to assess benzodiazepine-like discontinuation symptoms. This scale includes some of the symptoms that have been reported with ketamine withdrawal by case reports. In the absence of a more specific scale, all Phase 3 studies included the PWC-20 to systematically assess the risk of dependence with short and long-term use of esketamine nasal spray. The changes in withdrawal symptoms assessed by the PWC-20 after cessation of esketamine + oral AD treatment were consistent with observed changes in symptoms of depression and anxiety. Reported symptoms were primarily mild to moderate in severity. New worsening of depression symptoms was observed mostly in subjects who discontinued treatment due to lack of therapeutic response. Based on the PWC-20 results, there was no evidence suggestive of a distinct withdrawal syndrome at 1 or 2 weeks after cessation of esketamine treatment or at 1, 2, or 4 weeks after cessation of esketamine treatment.

## 5. Regulatory Issues and Assessment

### The Agency's Proposed REMS:

Should esketamine be approved, the REMS will be necessary to mitigate the risk of misuse and abuse and to prevent harm that could result from the adverse events of dissociation and sedation. At this time, labeling is being developed to address the concerns with elevated blood pressure.

Consistent with study protocols in the clinical program, the current Agency thinking is that to prevent harm such as falls or other accidents resulting from sedation and dissociation, the REMS would require that esketamine be self-administered under direct medical supervision and that patients then be monitored for a minimum of 2 hours post-dose. We are also recommending that after receiving esketamine, patients should not drive or operate heavy machinery for the rest of the day.

FDA is proposing the following REMS components to mitigate the risk of misuse, abuse and serious adverse outcomes from dissociation and sedation as a result of esketamine administration:

#### 1. Elements to assure safe use including:

- Prescriber training on the risks of esketamine and importance of monitoring patients after their dose is administered and the need to register patients
- Administration of esketamine only in certain health care settings that ensure patient monitoring by a healthcare provider for two hours after administration
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified to ensure that esketamine is not dispensed directly to patients and that patients are monitored
- Enrollment of patients who are treated with esketamine in a registry to better characterize the risks associated with esketamine administration and inform risk mitigation strategies

#### 2. An implementation system

#### 3. A timetable for submission of assessments

### **Administration only in certain healthcare settings**

Restricting the distribution of esketamine to certain healthcare settings would ensure that the patient is monitored by a healthcare provider until the sedation and dissociation subside. In the clinical development program, sedation resolved within 2 hours of dosing (with rare exceptions). Thus, it seems reasonable to monitor patients for 2 hours following administration of esketamine. This would prevent patients from engaging in activities that may be dangerous given these effects. Healthcare settings would also be required to counsel patients to refrain from driving for the remainder of the day of esketamine administration. To become certified, the healthcare setting must attest that HCPs are available to monitor patients.

### **Prescriber Training**

Prescribers would be educated about the risks of esketamine and the importance of monitoring patients after the dose is self-administered. In addition, prescribers would register their patients in the REMS program and monitor their patients for adverse events.

### **Enrollment of Patients in a Registry**

Enrollment of esketamine-treated patients in a registry would allow for the collection of additional data to characterize further the risks of esketamine post-administration. For example, the registry could collect adverse events that occur immediately after administration or between patient visits and provide insight into serious adverse outcomes associated with treatment. This would allow us to capture systematically information on events and potentially provide data that further characterizes adverse outcomes. Information collected from the registry may also be used to evaluate the risk mitigation strategies and determine the need for modification to the REMS or approved labeling.

As part of the enrollment process, patients would be informed of the risks and the need for patients to report adverse events to their provider between patient visits.

In conclusion, the FDA has the authority to require a REMS if additional measures beyond the labeling are necessary to ensure the benefits of a drug outweigh the risks. The committee will be asked if the FDA's proposed REMS will help ensure the safe use of esketamine and what components of this REMS are necessary to ensure that the benefits outweigh the risks.

## **6. Other Relevant Information**

None

## **III. REFERENCES**

Beardsley PM, Balster RL. Behavioral dependence upon phencyclidine and ketamine in the rat. *J Pharmacol Exp Ther.* 1987; 242(1):203-11.

Bowdle TA, Radant AD, Cowley DS, Kharasch ED, Strassman RJ, Roy-Byrne PP. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. *Anesthesiology.* 1998; 88(1): 82-88.

Broadbear JH, Winger G, Woods JH. Self-administration of fentanyl, cocaine and ketamine: effects on the pituitary-adrenal axis in rhesus monkeys. *Psychopharmacology.* 2004; 176:398-406.

Carroll ME, Stotz DC. Oral d-amphetamine and ketamine self-administration by rhesus monkeys: effects of food deprivation. *J Pharmacol Exp Ther.* 1983; 227:28-34.

Domino EF. Taming the ketamine tiger. 1965. *Anesthesiology.* 2010; 113(3): 678-684.

Ebert B, Mikkelsen S, Thorkildsen C, Borgbjerg FM. Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *Eur J Pharmacol*. 1997; 333(1):99-104.

Engelhardt W. Recovery and psychomimetic reactions following S-(+)-ketamine. *Anaesthetist* 1997; 46 (Suppl 1): S38-42.

Hancock PJ, Stamford JA. Stereospecific effects of ketamine on dopamine efflux and uptake in the rat nucleus accumbens. *Br J Anaesth*. 1999; 82:603-608.

Holtzman SG. Phencyclidine-like discriminative effects of opioids in the rat. *Journal of Pharmacology and Experimental Therapeutics*. 1980; 214 (3):614-619.

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994; 51(3): 199-214.

Lukas SE, Griffiths RR, Brady JV, Wurster RM. Phencyclidine-analogue self-injection by the baboon. *Psychopharmacology (Berl)* 1984; 83: 316-20.

Moreton JE, Meisch RA, Stark L, Thompson T. Ketamine self-administration by the rhesus monkey. *J Pharmacol Exp Ther* 1977; 203: 303-9.

Nishimura M, Sato K. Ketamine stereoselectively inhibits rat dopamine transporter. *Neurosci Lett*. 1999; 274:131-134.

O'Connor EC, Chapman K, Butler P, Mead AN. The predictive validity of the rat self-administration model for abuse liability. *Neuroscience and Biobehavioral Reviews*. 2011; 35:912-938.

Poling AD, White FJ, Appel JB. Discriminative stimulus properties of phencyclidine. *Neuropharmacology*. 1979; 18(5):459-463.

Shannon HE. Evaluation of phencyclidine analogs on the basis of their discriminative stimulus properties in the rat. *Journal of Pharmacology and Experimental Therapeutics*. 1981; 216 (3):543-551.

Smith DJ, Azzaro AJ, Zaldivar SB, Palmer S, Lee HS. Properties of the optical isomers and metabolites of ketamine on the high affinity transport and catabolism of monoamines. *Neuropharmacology*. 1981; 20:391-396.

Vollenweider FX, Leenders KL, Øye I, Hell D, Angst J. Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *Eur Neuropsychopharmacology* 1997; 7: 25-38.

Walgren JL, Carfagna MA, Koger D, Sgro M, Kallman MJ. Withdrawal assessment following subchronic oral ketamine administration in Cynomolgus macaques. *Drug Dev Res*. 2014; 75(3):162-71.

White JM, Ryan CF. Pharmacological properties of ketamine. *Drug Alc Review* 1996; 15: 145-155.

Yang C, Shirayma Y, Zhang JC, et al. R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. *Transl Psychiatry*. 2015; 5:e632.

Young AM, Herling S, Winger GD, Woods JH. Comparison of discriminative and reinforcing Effects of ketamine and related compounds in the rhesus monkey. *Natl. Inst. Drug Abuse Research Monogr. Series* 1981; 34: 173-9.

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

JOVITA F RANDALL-THOMPSON  
03/01/2019 02:36:21 PM

MARTIN S RUSINOWITZ  
03/01/2019 03:45:24 PM

SILVIA N CALDERON  
03/01/2019 03:46:53 PM

DOMINIC CHIAPPERINO  
03/01/2019 05:12:47 PM

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: February 25, 2019

To: Tiffany Farchione, MD  
Director (Acting)  
**Division of Psychiatry Products (DPP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Maria Nguyen, MSHS, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Domenic D' Alessandro, PharmD, MBA, CDE  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): SPRAVATO (esketamine)

Dosage Form and Route: Nasal spray, for intranasal use, CIII

Application Type/Number: NDA 211243

Applicant: Janssen Pharmaceuticals, Inc.

## 1 INTRODUCTION

On September 4, 2018, Janssen Pharmaceuticals, Inc., submitted for the Agency's review New Drug Application (NDA) 211243 for SPRAVATO (esketamine) nasal spray indicated for treatment-resistant depression (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on September 5, 2018 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SPRAVATO (esketamine) nasal spray.

## 2 MATERIAL REVIEWED

- Draft SPRAVATO (esketamine) nasal spray MG received on September 5, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 13, 2019 and again on February 20, 2019.
- Draft SPRAVATO (esketamine) nasal spray Prescribing Information (PI) received on September 5, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 13, 2019 and again on February 20, 2019.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

MARIA T NGUYEN  
02/25/2019 11:37:23 AM  
esketamine (SPRAVATO) NDA 211243 DMPP-OPDP MG FEB 2019

DOMENIC G DALESSANDRO  
02/25/2019 11:40:04 AM

BARBARA A FULLER  
02/25/2019 11:43:37 AM

LASHAWN M GRIFFITHS  
02/25/2019 01:03:30 PM

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Division of Epidemiology II**

**Drug Abuse Epidemiology Review**

**Date:** January 7, 2019

**Primary Reviewers:** Amy Seitz, PhD, MPH, Epidemiologist  
*Division of Epidemiology II*

Yulan Ding, PhD, Data Analyst  
*Division of Epidemiology II*

**Secondary reviewer:** Rose Radin, PhD, MPH, Acting Team Lead  
*Division of Epidemiology II*

**Tertiary reviewer:** Jana Mcaninch, MD, MPH, MS, Senior Medical Epidemiologist  
*Division of Epidemiology II*

**Subject:** **NDA 211243 – esketamine**  
Abuse and misuse of ketamine and associated harms

**\*\*This document contains proprietary drug use data and American Association of Poison Control Centers data obtained by FDA under contract. These data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology. All product codes must be redacted for public release.\*\***

## Table of Contents

Executive Summary .....	3
1. Introduction.....	4
2. Material and Methods .....	4
2.1 Drug Utilization .....	5
2.2 Pharmacoepidemiology Literature Search.....	5
2.3 National Survey on Drug Use and Health (NSDUH) .....	6
2.4 Monitoring the Future (MTF) .....	7
2.5 National Poison Data System (NPDS) Analysis.....	7
2.6 National Electronic Injury Surveillance System- Cooperative Adverse Drug Event Surveillance (NEISS-CADES) Analysis .....	8
2.7 FDA Adverse Event Reporting System (FAERS) Case Definition and Search Strategy .....	9
3. Results.....	10
3.1 Drug Utilization .....	10
3.2 Pharmacoepidemiology Literature Search.....	10
3.3 National Survey on Drug Use and Health (NSDUH) .....	11
3.4 Monitoring the Future (MTF) .....	12
3.5 National Poison Data System (NPDS) Analysis.....	13
3.6 National Electronic Injury Surveillance System- Cooperative Adverse Drug Event Surveillance (NEISS-CADES) Analysis .....	15
3.7 FDA Adverse Event Reporting System (FAERS) .....	16
4. Discussion.....	18
5. Conclusions.....	20
Appendices.....	22
Appendix A. NPDS Definitions of Exposure Reasons .....	22
Appendix B. NPDS Definition for Medical Outcome .....	23
Appendix C. NPDS Generic and Product Codes .....	24
Appendix D. NEISS-CADES Definitions of Adverse Drug Events.....	25
Appendix E. FDA Adverse Event Reporting System (FAERS).....	26
7. References.....	27

## EXECUTIVE SUMMARY

Ketamine is a rapidly acting dissociative anesthetic, marketed in the U.S. since the 1970s for use in humans and animals. For many decades, ketamine has been reported as a drug of abuse, and in 1999, ketamine and its salts were designated as Schedule III substances under the Controlled Substances Act. Ketamine is abused for its dissociative and hallucinogenic effects and has been termed a “club drug” or “party drug” because of its popularity for use at nightclubs and raves. According to the DEA, most of the ketamine illegally distributed in the U.S. is diverted or stolen from legitimate sources such as veterinary clinics or smuggled from Mexico and then sold or shared at parties or nightclubs.

For this review, drug utilization data are referenced from a recent DPV II and DEPI Drug Use review<sup>a</sup> to provide context for recent data on ketamine abuse. Previously published literature and national estimates from National Survey on Drug Use and Health and the Monitoring the Future survey are provided to understand the prevalence of ketamine abuse. We also provide information on ketamine abuse and associated adverse outcomes, analyzing data from calls to U.S. poison centers (National Poison Data System), emergency department visits (National Electronic Injury Surveillance System-Cooperative Adverse Drug Event), and spontaneous adverse event reports from the FDA Adverse Drug Event Reporting System (excerpted from a recent DPV II memo on ketamine abuse in October 2017<sup>b</sup>).

Based on national sales distribution patterns of ketamine vials (excluding veterinary sales), ketamine utilization appears to be largely in the hospital setting. Ketamine sales increased approximately 72% from 2013 to 2017 overall and sales to clinic settings, specifically, more than doubled during this five-year period. Numerous off-label uses of ketamine have been proposed and implemented, including treatment resistant depression, and recent literature suggests growth in some of these off-label uses of ketamine.

National survey data and the published literature indicate that ketamine abuse is relatively uncommon in the general population, with a reported lifetime prevalence of 1.3% among persons age 12 years and older, which is lower than that for other hallucinogens such as ecstasy and LSD (Acid). Among 12<sup>th</sup> graders, the annual prevalence of ketamine use has declined from 2.5% in 2000 to 1.2% in 2017. Exposure calls to U.S. poison centers involving ketamine abuse or misuse also declined slightly from 2013 to 2017 (176 calls in 2013 to 116 calls in 2017), despite the growth in non-veterinary ketamine sales. Single-substance exposure calls to poison control centers involving ketamine abuse or misuse were most commonly associated with minor or moderate health effects, and there were no deaths identified among these calls. In a representative sample of approximately 60 U.S. emergency departments, there were 44 ketamine-related ED cases in 2016-2017, corresponding to an estimated 669 visits nationally. Of the 44 ketamine-related ED cases, 35 (81.5%) were classified as abuse. Only six (17.1%) of these cases resulted in hospitalization. From 2015-2017, the FDA Adverse Event Reporting System (FAERS) received 17 reports of death involving ketamine abuse. Of note, only one of these reports listed ketamine as the only suspected drug, and the drug-event causal association has not been assessed for any of these FAERS cases.

---

<sup>a</sup> Mundkur M. Adverse Events with Repeated Off-label Use of Ketamine. In DARRTS 12/21/2018, Ref ID 4367425.

<sup>b</sup> Patel C. Abuse-related data for WHO questionnaire. In DARRTS 10/2/2017, Ref ID 4161583.

Overall, this analysis suggests that ketamine abuse continues to occur but has remained relatively limited with modest associated harms. The available data are insufficient to determine the extent to which U.S. pharmaceutical ketamine for humans contributes to abuse, relative to ketamine that is smuggled into the country or diverted from veterinary settings. Nonetheless, the risks of abuse and associated harms are important considerations in determining appropriate risk mitigation strategies and post marketing surveillance for esketamine, if approved.

## 1. INTRODUCTION

The Division of Epidemiology II (DEPI) was asked by the FDA Controlled Substances Staff to provide current information on ketamine abuse and misuse and associated adverse events, for consideration at the joint meeting of the Psychopharmacologic Drugs and the Drug Safety and Risk Management Advisory Committees on February 12, 2019. The committees will discuss the New Drug Application 211243 for esketamine, an enantiomer of ketamine, for treatment resistant depression in adults.

Ketamine is a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptor and is a rapidly acting dissociative anesthetic marketed in the U.S. since the 1970s for use in humans and animals. In humans, it is indicated for 1) diagnostic and surgical procedures that do not require skeletal muscle relaxation, as the sole anesthetic, 2) administration prior to other general anesthetic agents, and 3) supplementing low-potency agents, such as nitrous oxide.(1) In the U.S., injectable ketamine is the only approved formulation for humans. Since the time of its approval, numerous off-label uses of ketamine have been proposed and implemented, including, but not limited to, treatment of complex-regional pain syndrome (CRPS), chronic pain, and treatment resistant depression.(2-6) Emerging literature describes some of these off-label uses of ketamine,(3, 7) providing some standardization, but in practice, treatment regimens can vary.

Ketamine has been reported in the literature as a drug of abuse for many decades, and in 1999, ketamine and its salts were designated as Schedule III substances under the Controlled Substances Act. Also known as “Special K” and by multiple other slang terms, ketamine is abused for its dissociative and hallucinogenic effects and has been termed a “club drug” or “party drug” because of its popularity for use at nightclubs and raves.(8, 9) Due to its sedative and amnesic effects, ketamine has also been used for facilitating sexual assault and nonconsensual sexual intercourse.(8, 9) Powdered ketamine can be snorted or smoked, and liquid ketamine can be injected, mixed into drinks, placed on materials to be smoked, or evaporated by heating and ground into a powder.(8, 9) According to the DEA, most of the ketamine illegally distributed in the U.S. is diverted or stolen from legitimate sources such as veterinary clinics or smuggled from Mexico and then sold or shared at parties or nightclubs.(8)

The purpose of this review is to provide current information on the scope and patterns of ketamine abuse and associated harms in the U.S.

## 2 MATERIAL AND METHODS

This review includes information from the epidemiologic literature, the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event (NEISS-CADES) database, the

American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS), the National Survey on Drug Use and Health (NSDUH), and the Monitoring the Future (MTF) survey. Also, we considered estimates of annual U.S. sales of ketamine vials analyzed by the DEPI-Drug Use team for a previous review<sup>c</sup> and FDA Adverse Event Reporting System (FAERS) results analyzed by the Division of Pharmacovigilance for a previous memo<sup>d</sup>.

The purpose for including multiple data sources is to provide a robust description of ketamine abuse and misuse through complementary data sources because each of these data sources has strengths and limitations. Details on each data source are provided below. Definitions of misuse and abuse vary by data source and will be described as appropriate. The following standard regulatory definitions of misuse/abuse were applied throughout this review, unless otherwise indicated:(10, 11)

**Misuse:** the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse

**Abuse:** the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect

## 2.1 DRUG UTILIZATION

Drug utilization data provide context for data on misuse and abuse of pharmaceutical products. For drug utilization information, we referenced the recent integrated review by the Division of Pharmacovigilance (DPV) II and DEPI-Drug Use<sup>c</sup>. This review focused on the hepatobiliary and cognitive impairment adverse events associated with repeated off-label use of ketamine and also provided results of a sales and distribution analysis from the IQVIA, National Sales Perspectives (NSP) database.

## 2.2 PHARMACOEPIDEMIOLOGY LITERATURE SEARCH

Using the search terms and parameters described in **Table 2.2**, DEPI II conducted a literature search using PubMed.gov to identify recent published observational epidemiologic studies on ketamine misuse and abuse, and their consequences (e.g., addiction/ substance use disorder, overdose).

---

<sup>c</sup> Mundkur M. Adverse Events with Repeated Off-label Use of Ketamine. In DARRTS 12/21/2018, Ref ID 4367425.

<sup>d</sup> Patel C. Abuse-related data for WHO questionnaire. In DARRTS 10/2/2017, Ref ID 4161583.

<b>Table 2.2 Literature Search Strategy</b>	
<b>Date of Search</b>	November 29, 2018
<b>Database</b>	PubMed
<b>Search Terms</b>	Ketamine, ketalar, abuse, addiction, diversion, substance use disorder, misuse
<b>Search parameters</b>	(((((ketamine[tw] OR ketalar) AND (abuse[tw] OR abuses[tw] OR addiction[tw] OR addictions[tw] OR diversion[tw] OR "drug dependence"[tw] OR "substance use disorder"[tw] OR "substance use disorders"[tw] OR substance-related disorders[tw] OR substance-related disorder[tw] OR "drug misuse"[tw] OR "drug misuses"[tw]))) AND English[Language]) NOT (("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))) AND ("2016"[Date - Publication] : "2018"[Date - Publication]))) AND ("2016/01/01"[Date - Publication] : "2018/11/28"[Date - Publication])
<b>Years included in search</b>	2016-2018
<b>Other criteria</b>	English language articles, observational epidemiologic studies
Note: In addition to the search strategy above, we mined primary sources from secondary references	

### 2.3 NATIONAL SURVEY ON DRUG USE AND HEALTH (NSDUH)

The National Survey on Drug Use and Health (NSDUH) is an annual survey conducted nationwide by the Substance Abuse and Mental Health Services Administration (SAMHSA). NSDUH collects information on drug use, mental health, and other health related issues with the goal of providing accurate, nationally representative data about the use of alcohol, tobacco, other drugs and substance use and misuse. NSDUH also aims to “assess the consequences of substance use and misuse.” Information is collected from civilian, noninstitutionalized participants aged 12 years and older. Population subgroups not covered by the survey include individuals residing within institutional facilities (e.g., jails, nursing homes), as well as those without a permanent address (e.g., homeless individuals). The survey is conducted in a face-to-face manner, and during the year 2017, the interview response rate of 50.4% included 68,032 completed interviews.(12) In NSDUH, misuse is defined as “*use in a way not directed by a doctor, including use without a prescription of one’s own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.*” However, because NSDUH categorizes ketamine as a hallucinogen and includes it in the same section with illicit drugs such as cocaine and heroin, misuse of ketamine is termed “*ketamine use.*”(12, 13)

A partial redesign of the NSDUH questionnaire occurred in 2015 so trends are limited for many estimates.(12) We extracted and summarized information on hallucinogens and ketamine use from the most recent publicly available reports of NSDUH results.(12, 13)

## 2.4 MONITORING THE FUTURE (MTF)

The Monitoring the Future survey (MTF) is an annual survey monitoring the “behaviors, attitudes, and values of American secondary school students, college students, and young adults.” The survey is supported with grants from the National Institute on Drug Abuse, National Institutes of Health.(14)

MTF uses the term “misuse” for prescription medications to mean “use outside of a doctor’s orders.” They describe ketamine abuse and misuse as the annual prevalence of use, meaning “the percent of the study sample that report using a drug once or more during a given period- i.e. past 12 months.”(15) We extracted and summarized the findings relating to ketamine from the published report of 2017 MTF survey results.

## 2.5 NATIONAL POISON DATA SYSTEM (NPDS) ANALYSIS

The NPDS database includes calls from individuals, healthcare professionals, and other interested persons regarding exposures to prescription drugs, over-the-counter medications, unapproved products, and other substances, to all poison control centers in the U.S.(16) NPDS is managed by the American Association of Poison Control Centers (AAPCC). The AAPCC Annual Report contains additional information.(17)

The NPDS calls for exposures may result in provision of information or advice regarding medical management, and AAPCC staff managing these calls undergo training to standardize documentation across centers. Documentation of calls includes detail on the drug(s), patient characteristics, route of exposure, reported reasons for exposure, level of care received, medical, and other variables. Reasons for exposure are categorized into groups by AAPCC, and include such categories as “intentional”, “unintentional,” the former encompassing the subgroups of intentional misuse, abuse, suspected suicide or unknown intent. Additional detail regarding the definition of these variables is provided in **Appendix A** of this review. Medical outcomes are based on all information known at the conclusion of the case and coded as “No effect,” “Minor effect,” “Moderate effect,” or “Major effect.” *Medical outcome* was characterized for the subset of calls with a “Related” clinical effect. NPDS defines “Related” clinical effects as exposures where the following criteria are satisfied: the timing and severity of clinical effects are reasonable for the reported exposure, the clinical effect is consistent with the anticipated substance, and the clinical assessment is made by a physician. Exposures with “Related” clinical effects were identified if any listed clinical effect for a given exposure call involving the drug of interest was designated as “(R).” If not appropriate or possible to follow a case, the case is labeled as “case not followed to known outcome.” Additional detail regarding the definition of these variables is provided in **Appendix B** of this review. Follow-up calls to NPDS from the same exposure event are recorded as a single exposure; a person can have more than one call for an exposure to the same substance if they happen at different times.

We searched NPDS using the criteria described in **Table 2.3**. For the purposes of this descriptive analysis, we included all “closed cases” of human exposure to ketamine, January 1, 2013 to December 31, 2017, including cases with multiple drug exposures. *Closed cases* have been through quality assurance procedures by AAPCC. We identified generic and product codes for pharmaceutical preparations for ketamine, including human and veterinary products from the

U.S. and other countries (n=105 generic and product codes), using Micromedex® Solutions (**Appendix C**).

Analysis of NPDS consisted of tabulating counts of ketamine exposure calls by year. We separated intentional exposures from unintentional exposures/adverse reactions and cross-tabulated various characteristics of the exposure--i.e., reason for exposure, related medical outcome, number of substances involved, and route of exposure--by year. These analyses were replicated by a second analyst for quality assurance.

Database	National Poison Data System
Report name	Case Log (Generic and Product Code)
Month/year of query	12/2018
Date range for query	01/01/2013- 12/31/2017
Call type	Exposure
Case status	Closed
Species	Human
Exposure reason	All
Age	0-120 years
Product codes	See Appendix C of this review

## **2.6 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM- COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES) ANALYSIS**

DEPI consulted with Centers for Disease Control and Prevention to identify ketamine-related adverse drug event (ADE) cases in the NEISS-CADES database. NEISS-CADES data comprise a national stratified probability sample of approximately 60 hospitals with a minimum of 6 beds and a 24-hour ED in the U.S. and its territories. The NEISS-CADES project, which has been described in detail elsewhere, is a joint effort of the Centers for Disease Control and Prevention, the U.S. Consumer Product Safety Commission, and the U.S. Food and Drug Administration.(18-21) In brief, trained coders located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed drug related adverse events, to report up to 4 medications implicated in each adverse event, and to record narrative descriptions of the incident.

NEISS-CADES has historically focused exclusively on ED visits due to use of medications for a therapeutic indication, or unintended medication exposures by young children. However, in 2016 NEISS-CADES surveillance activities were expanded to represent a wider spectrum of pharmaceutical-related harm, encompassing ED visits resulting from abuse, self-harm, overdoses without indication of intent, therapeutic misuse and assault, in addition to therapeutic adverse drug events.

The 2016-2017 NEISS-CADES database was searched for ADEs related to ketamine, including cases of nonmedical use (i.e., abuse, therapeutic misuse, or overdose with unknown intent), therapeutic adverse event, assault, and self-harm/suicide (search date: November 28, 2018). Definitions for these case types are provided in **Appendix D** of this review. National projections of ED visits for ADEs associated with ketamine were estimated using hospital-based sample weights. National projections of the number of cases can only be made when there are sufficient

number of cases ( $\geq 20$  cases in the sample and  $\geq 1,200$  cases in the national estimate) and level of variability (coefficient of variation  $\leq 0.3$ ).

## 2.7 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) CASE DEFINITION AND SEARCH STRATEGY

FAERS is a database that contains spontaneously reported information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS was previously searched by DPV II for ketamine and its abuse, and the results were included in an October 2017 review memo<sup>e</sup>. The description of the FAERS search below is from this memo.

“For the purposes of this descriptive analysis, we included all serious U.S. reports coded to the Standardized MedDRA Query (SMQ), *Drug abuse, dependence, and withdrawal (SMQ) Broad* and listing ketamine-containing product as a suspect product.

<b>Table 2.7. Ketamine FAERS Search Strategy*</b>	
Date of Search	September 11, 2017
Time Period of Search	FDA initial received date: January 1, 2015 <sup>†</sup> - Completed date: <sup>‡</sup> September 11, 2017
Search Type	FBIS Quick Query
Product Terms <sup>f</sup>	Product active ingredient: Norketamine; Baclofen\clonidine\diclofenac\gabapentin\ketamine\prilocaine; Bupivacaine\cyclobenzaprine\fluticasone\gabapentin\ketamine\ketoprofen; Ketamine hydrochloride; Bupivacaine\clonidine\cyclobenzaprine\flurbiprofen\ketamine; Amitriptyline\baclofen\bupivacaine\diclofenac\gabapentin\ketamine; N-Ethylorketamine; Baclofen\gabapentin\ketamine\ketoprofen; esketamine; Ketamine; Amitriptyline\gabapentin\ketamine; Esketamine hydrochloride; Diazepam\diclofenac sodium\gabapentin\ketamine; Deschloroketamine
MedDRA Search (Version 20.0)	<i>Drug abuse, dependence, and withdrawal (SMQ) Broad</i> search
Other Filters	Case outcome: Serious Country (Derived): USA
MedDRA= Medical Dictionary for Regulatory Activities, SMQ = Standardized MedDRA Query * See <b>Appendix E</b> of this review for a description of the FAERS database is included in the integrated review by DPV II and DEPI Drug Use, included as an appendix to this briefing document. <sup>†</sup> The search dates used represent recent use and were requested by the consultant – the Controlled Substance Staff. <sup>‡</sup> FDA data entry completion date.	

<sup>e</sup> Patel C. Abuse-related data for WHO questionnaire. In DARRTS 10/2/2017, Ref ID 4161583.

<sup>f</sup> Product terms were used to encompass all potential formulations for off-label use

### 3 RESULTS

#### 3.1 DRUG UTILIZATION

As described in the recent DPV II and DEPI Drug Use review<sup>§</sup>, the estimated total number of ketamine vials sold from manufacturers to all settings of care increased approximately 72% from 2013 to 2017, from 1.2 million vials to 2.1 million vials, respectively. In 2017, the largest proportion of ketamine vials were sold to non-federal hospitals, at approximately 54%, followed by 37% and 9% of vials sold to clinics and all other channels, respectively. Although manufacturer sales of ketamine to all channels of distribution increased; the increase was most notable in the clinic settings, where the number of vials sold more than doubled, from an estimated 332,000 vials sold in 2013 to 765,500 vials sold in 2017. Veterinary sales were not included in this analysis.

Data on indication for use were not available for ketamine, however recent publications propose numerous off-label uses(2-6) and guidelines for off-label use,(3, 7) suggesting an increasing interest in ketamine for off-label uses.

#### 3.2 PHARMACOEPIDEMOLOGY LITERATURE SEARCH

A total of 200 articles were identified using the search strategy described in **Table 2.2**. Of these 200 articles, 36 were determined to be relevant to this review, and additional articles were identified by mining primary sources through these articles. Articles included reviews, observational epidemiology studies, and ecologic studies. Individual case reports and case series were identified in the search but not included as part of the epidemiologic review.

Published reviews and other studies indicate that ketamine abuse began soon after its approval as an anesthetic agent in 1970, but its popularity at dance clubs and raves rose in the 1980s and 1990s.(22-24) Ketamine is described as a drug abused as a recreational drug worldwide, often in the setting of electronic music parties and dance clubs, and has also been used for drug-facilitated sexual assault.(22-24) Illicit ketamine is available as aqueous solution, capsules, powder, crystals and tablets.(22) Adulterants are often added to the illicit formulations, especially in tablets. Ketamine is also used as an adulterant of ecstasy.(22, 25) Ketamine can be abused by insufflating powder, but ingesting, smoking or injecting are also routes of administration for abuse, depending on the form.(9, 22, 24)

Multiple articles describe harms from ketamine abuse. One review of published case studies and case series focused on people in Hong Kong who abuse ketamine, describing urological complications, neuropsychiatric complications, hepatobiliary complications, and gastrointestinal complications.(26) One study from Taiwan described sexual and bladder dysfunction associated with ketamine abuse among participants presenting at clinics and men who encountered law enforcement.(27)

Original observational epidemiology studies described patterns of illegal drug use, including ketamine abuse, in specific populations such as people who had used ecstasy in the past year, men who have sex with men and persons attending dance clubs.(28-30) The prevalence of ketamine abuse varied by the population studied. For example, in a study conducting secondary

---

<sup>§</sup> Mundkur M. Adverse Events with Repeated Off-label Use of Ketamine. In DARRTS 12/21/2018, Ref ID 4367425.

analysis of NSDUH data, 6.5% of people ages 12-34 years who had used ecstasy in the past-year (N=332,560) reported past-year ketamine use in 2013-2014.(30) In a cohort of Australian gay and bisexual men (N=1,710), the twelve-month incidence rate of ketamine use (i.e., abuse or misuse) was 2.1 per 100 person-years, and varied by age group from 4.1 per 100 person-years for ages 16-24 years to 0.98 per 100 person-years for persons 40 years and older.(29) Multiple other studies report epidemiology of ketamine abuse and other illicit drugs in specific populations, many using convenience samples in non-U.S. populations.(31-33)

### 3.3 NATIONAL SURVEY ON DRUG USE AND HEALTH (NSDUH)

In 2017, 1.3% of NSDUH survey respondents aged 12 or older reported using ketamine during their lifetime, corresponding to an estimated 3.4 million U.S. residents (Table 3.3a). Those aged 18-25 years had the highest prevalence, with 1.8% in 2017 reporting lifetime ketamine use. This was much lower compared to lifetime use of other hallucinogens. For example, 7.0% of respondents aged 12 years and older and 12.0% of respondents aged 18-25 years reported lifetime use of ecstasy. For LSD, 9.6% of respondents aged 12 years and older and 9.1% of respondents aged 18-25 years reported lifetime use. For hallucinogens overall (including ketamine), 15.5% of respondents aged 12 years and older and 17.1% of respondents aged 18-25 years reported lifetime use. For additional context, among respondents 12 years and older 45.2% of respondents reported lifetime use of marijuana, 14.9% reported lifetime use of cocaine, and 1.9% reported lifetime use of heroin in 2017 (data not shown).

		Aged 12 years or older	Aged 12-17 years	Aged 18 years or older	Aged 18-25 years	Aged 26 years or older
Ketamine	Percent reporting lifetime use	1.3	0.2	1.4	1.8	1.3
	Estimated number (in thousands)	3,463	46	3,417	632	2,785
Ecstasy	Percent reporting lifetime use	7.0	1.0	7.7	12.0	7.0
	Estimated number (in thousands)	19,173	257	18,915	4,105	14,811
LSD (Acid)	Percent reporting lifetime use	9.6	1.5	10.4	9.1	10.6
	Estimated number (in thousands)	26,069	364	25,705	3,125	22,581
Hallucinogens (including ketamine)	Percent reporting lifetime use	15.5	2.8	16.7	17.1	16.7
	Estimated number (in thousands)	42,072	700	41,372	5,859	35,513

Source: "Table 1.96A Specific Hallucinogen, Inhalant, Needle, Heroin, and other Drug Use in Lifetime among Persons Aged 12 or Older, by Age Group: Numbers in Thousands, 2016 and 2017 and Table 1.96B Specific

Hallucinogen, Inhalant, Heroin and other Drug Use in Lifetime among Persons Aged 12 or Older, by Age Group: Percentages, 2016 and 2017; SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2016 and 2017”(13)

The 2017 NSDUH Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health does not report past month or past year ketamine use separately but describes past month hallucinogen use, a category which includes ketamine, LSD, ecstasy and others.(12) Table 3.3b shows the estimated prevalence of past month use of hallucinogens, by age group, in 2017. Not surprisingly, past month estimates are considerably lower than lifetime prevalence estimates in all age groups (Table 3.3a).

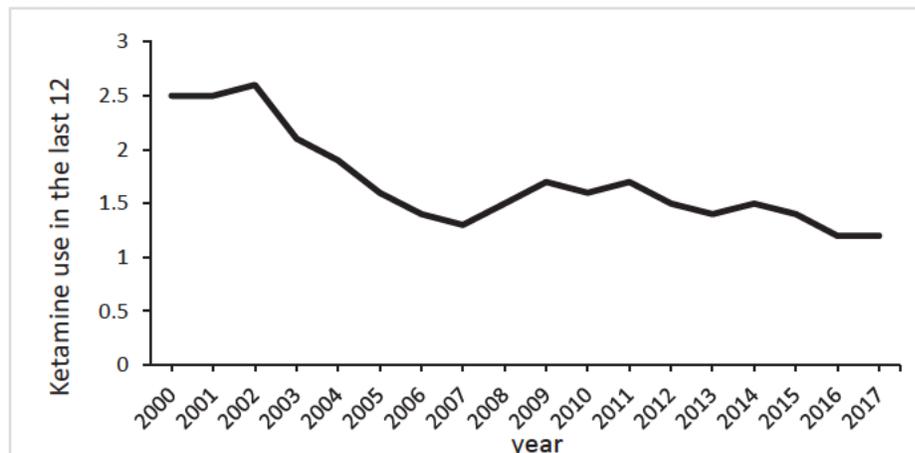
	Aged 12 years or older	Aged 12 to 17 years	Aged 18 to 25 years	Aged 26 years or older
Percent using in past month	0.5	0.6	1.7	0.3
Number (in thousands)	1,400	143	594	701

Source: “Figure 11. Numbers of Past Month Illicit Drug Users among People Aged 12 or Older: 2017. and Figure 17. Past Month Hallucinogen Use Among People Aged 12 or Older, by Age Group: Percentages, 2017. SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2017.(12)

### 3.4 MONITORING THE FUTURE (MTF)

Among 12<sup>th</sup> graders, the estimated annual prevalence of ketamine use declined from 2.5% in 2000 to 1.2% in 2017 (1.4% for males and 0.7% for females), as shown in **Figure 3.4**.(15)

**Figure 3.4 Annual prevalence of ketamine use among 12th graders, Monitoring the Future, 2000-2017**



Note: In order to maintain trends during questionnaire changes, estimates are based on varying proportions of the sampled populations in some years. See MTF documentation for details(15)

Source: The Monitoring the Future study, the University of Michigan, Table 5-2. Long-Term Trends in Annual Prevalence of Use of Various Drugs for Grade 12(15)

Estimated annual prevalence of use for ketamine and select additional drugs from 2008 to 2017 are presented in **Table 3.4** for context. The data suggest that, among 12<sup>th</sup> graders, the percentage who used ketamine in the last 12 months was generally lower than for other drugs, with the exception of heroin. In 2017, the he estimated annual prevalence of use for ketamine was most similar to that of Ritalin and inhalants. From 2007 to 2017, the percentage of 12th graders reporting past-year use of ketamine, Ritalin, OxyContin, Vicodin, heroin, inhalants, over the counter cough/cold medicines and cocaine all declined slightly.

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
<b>Ketamine</b>	1.5	1.7	1.6	1.7	1.5	1.4	1.5	1.4	1.2	1.2
<b>Ecstasy<sup>a</sup></b>	--	--	--	--	--	--	5.0	3.6	2.7	2.6
<b>Ritalin<sup>b</sup></b>	3.4	2.1	2.7	2.6	2.6	2.3	1.8	2.0	1.2	1.3
<b>OxyContin<sup>b</sup></b>	4.7	4.9	5.1	4.9	4.3	3.6	3.3	3.7	3.4	2.7
<b>Vicodin<sup>b</sup></b>	9.7	9.7	8.0	8.1	7.5	5.3	4.8	4.4	2.9	2.0
<b>Heroin</b>	0.7	0.7	0.9	0.8	0.6	0.6	0.6	0.5	0.3	0.4
<b>LSD</b>	2.7	1.9	2.6	2.7	2.4	2.2	2.5	2.9	3.0	3.3
<b>Inhalants</b>	3.8	3.4	3.6	3.2	2.9	2.5	1.9	1.9	1.7	1.5
<b>OTC Cough/Cold Medicines<sup>c</sup></b>	5.5	5.9	6.6	5.3	5.6	5.0	4.1	4.6	4.0	3.2
<b>Cocaine</b>	4.4	3.4	2.9	2.9	2.7	2.6	2.6	2.5	2.3	2.7
<b>Marijuana/Hashish</b>	32.4	32.8	34.8	36.4	36.4	36.4	35.1	34.9	35.6	37.1

Note: In order to maintain trends during survey changes, data for multiple years and multiple drugs are based on varying proportions of the sampled populations. See MTF documentation for details.(15)  
<sup>a</sup> This question was revised in 2014 and earlier years are not presented due to this change.  
<sup>b</sup> Only use not under a doctor's orders is included here.  
<sup>c</sup> Only use "to get high" is included here.

Source: The Monitoring the Future study, the University of Michigan, Table 5-2. Long-Term Trends in Annual Prevalence of Use of Various Drugs for Grade 12

### 3.5 NATIONAL POISON DATA SYSTEM (NPDS) ANALYSIS

From January 1, 2013 to December 31, 2017 there were 1,454 ketamine exposure calls to U.S. poison control centers. The majority of these calls (67.8%) were due to intentional exposures, and intentional abuse and misuse contributed to more than half of all exposure calls (53.5%). Characteristics of all ketamine exposure calls and abuse and misuse exposure calls are described in **Table 3.5a** and **3.5b**, respectively.

<b>Table 3.5a. Ketamine Exposure calls in the U.S. National Poison Data System, January 1, 2013 to December 31, 2017</b>						
<b>Year</b>	<b>2013 N</b>	<b>2014 N</b>	<b>2015 N</b>	<b>2016 N</b>	<b>2017 N</b>	<b>Total</b>
<b>Total Exposures</b>	309	327	308	260	250	1454
<b>Intentional</b>	208	227	223	164	164	986
Suspected suicide	24	32	32	35	38	161
Abuse	169	174	165	114	109	731
Misuse	7	12	14	7	7	47
Unknown	8	9	12	8	10	47
<b>Unintentional</b>	62	63	43	57	55	280
<b>Adverse Reactions</b>	22	21	17	23	21	104
<b>Other</b>	11	7	17	7	6	48
<b>Unknown</b>	6	9	8	9	4	36

Source: American Association of Poison Control Centers- National Poison Data System, January 1, 2013-December 31, 2017.

Among the 778 intentional abuse and misuse ketamine exposure calls, a little more than half (53.4%) involved only one substance. Among cases with only one substance, moderate effect was the most frequent related clinical effect, and ingestion was the most commonly reported route of exposure. Inhalation was the second most frequent route of exposure. Multiple routes of exposure could be selected for a single case. These descriptive characteristics for intentional abuse and misuse exposures are shown below in **Table 3.5b**.

<b>Table 3.5b. Descriptive Case Characteristics of Ketamine Intentional Abuse and Misuse Exposure Calls in the U.S. National Poison Data System, January 1, 2013 to December 31, 2017</b>						
<b>Year</b>	<b>2013</b>	<b>2014</b>	<b>2015</b>	<b>2016</b>	<b>2017</b>	<b>Total</b>
<b>Total Intentional Abuse and Misuse</b>	176	186	179	121	116	778
<b>Number of substances</b>						
Single	103	96	99	61	57	416
Multiple	73	90	80	60	59	362
<b>Related Medical Outcome (single-substance exposures only)<sup>a,b</sup></b>						
No clinical effect	0	0	0	0	0	0
Minor effect	25	17	21	14	11	88
Moderate effect	51	37	43	23	24	178
Major effect	1	10	6	8	5	30
Death <sup>c</sup>	0	0	0	0	0	0
Other <sup>d</sup>	11	9	9	5	7	41
<b>Route of exposure (single-substance exposures only)<sup>a,e</sup></b>						
Ingestion	41	43	39	29	22	174
Inhalation	30	34	39	17	24	144
Dermal	1	2	1	0	0	4
Parenteral	23	9	9	8	8	57
Other <sup>f</sup>	12	11	13	9	6	51
<sup>a</sup> Related medical outcome and route of exposure were characterized only for the subset of patients with single-substance exposure <sup>b</sup> Medical outcomes among individuals with a related clinical effect. <sup>c</sup> Includes “death” and “death, indirect report” <sup>d</sup> Other includes: Not followed, judged as nontoxic exposure (clinical effects not expected), Not followed, minimal clinical effects possible (no more than minor effect possible) <sup>e</sup> Multiple routes are possible for a single exposure. <sup>f</sup> Other (Route) includes: aspiration (with ingestion), ocular, other, other (not ingestion, bite/sting or dermal), otic, rectal, unknown, and vaginal						

Source: American Association of Poison Control Centers- National Poison Data System, January 1, 2013-December 31, 2017.

### **3.6 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM- COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES) ANALYSIS**

In 2016-2017, based on 44 surveillance cases, there were an estimated 669 (95% CI 949-3,628) ED visits nationally for adverse events related to ketamine. Of the 44 cases identified in the surveillance sample, 35 (81.5% [95% CI 61.0-100.0%]) were classified as abuse. National estimates of the number of ED visits due to ketamine abuse were not stable due to a high coefficient of variation (>0.30). Of the 35 cases involving abuse, six were hospitalized. Routes of ketamine abuse included swallowing, inhaling/snorting and IV injection; however, in most cases the route of administration was unknown. No cases were found for overdose without indication of intent or therapeutic misuse. **Table 3.6** describes the NEISS-CADES cases for ketamine related ED cases.

Most (60%) of the 35 abuse cases also involved illicit drugs (cocaine, heroin, marijuana, methamphetamine, fentanyl, or other), alcohol, or both. Of all the ketamine abuse cases, 10

involved another approved medication, dietary supplement, homeopathic product, or vaccine (data not shown).

<b>Table 3.6 Ketamine Related Emergency Department Cases, National Electronic Injury Surveillance System- Cooperative Adverse Drug Event Surveillance Sample, 2016-2017</b>				
	Abuse	Therapeutic Use	Assault	Total
<b>Total</b>	35	8	1	44
<b>Route</b>				
Oral	1	0	1	2
Nasal	6	1	0	7
Injection	3	4	0	7
Infusion	0	1	0	1
Unknown	25	2	0	27
<b>Medical disposition</b>				
Hospitalized	6	1	0	7
Not hospitalized <sup>a</sup>	29	7	1	37
<sup>a</sup> Includes “left without being seen LWBS/ left against medical advice LAMA” (n=3 for abuse)				

Source: National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES), 2016-2017.

### 3.7 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

Below is a summary of results of the FAERS search conducted by DPV II for a memo on ketamine abuse in October 2017<sup>h</sup>.

The FAERS search from January 1, 2015 to September 11, 2017 for serious U.S. cases of ketamine associated with drug abuse retrieved 39 reports. Abuse reports for ketamine include all reports coded under the MedDRA *Drug abuse, Dependence, and Withdrawal (SMQ) Broad*, including reports coded to the preferred term (PT) Intentional product misuse. These reports have not been manually reviewed and, as such, the data may contain duplicates. Further, a causal association of the reported adverse event(s) or reported outcome(s) with ketamine exposure was not determined for this assessment. The 39 cases were received by FDA from 2015 to 2017 although some of these cases had occurred in previous years. Only 13 reports included information on event year, and these years ranged from 2013 to 2017. Approximately 43.6% (17/39) of the reports reported an outcome of death, and 53.8% (21/ 39) of the reports involved hospitalization. Deaths and hospitalizations were not mutually exclusive case outcomes. **Table 3.7** provides descriptive characteristics of the ketamine FAERS reports.

<sup>h</sup> Patel C. Abuse-related data for WHO questionnaire. In DARRTS 10/2/2017, Ref ID 4161583.

**Table 3.7. Descriptive Case Characteristics of U.S. FAERS Reports of Ketamine Associated with Abuse,\* Received by FDA from January 1, 2015 to September 11, 2017 (N=39)†**

Sex	Male Female Unknown	16 15 8
Age (years)	1 – 12 13 – 18 19 – 40 41 – 60 61 and older Unknown	2 3 19 4 1 10
Reporter type	Health care professional‡ Consumer Unknown	32 5 2
Report type	Expedited (15-Day) Direct Non-expedited	36 2 1
Reported route (n=15)	Nasal/inhalation Intramuscular Intravenous Parenteral Oral/Buccal Transdermal	4 4 2 1 3 1
MedDRA preferred terms§ (n=37)	Drug use disorder Toxicity to various agents Overdose Unresponsive to stimuli Sedation Biliary dilatation Drug withdrawal syndrome Off label use Accidental overdose Hydronephrosis Intentional product misuse Pain	18 11 8 6 5 4 4 4 3 3 3 3

\* All serious reports coded under the MedDRA *Drug abuse, dependence, and withdrawal (SMQ) Broad* were included.

† These reports have not been manually reviewed and, as such, may include duplicates.

‡ Healthcare professional reports include those indicating the reporter's qualifications as a healthcare professional, physician, or a pharmacist.

§ Most frequently reported MedDRA preferred terms with  $n \geq 3$ . A report may include more than one preferred term.

Reports were most frequently reported in the 19 – 40 year-old age group. The majority of the reporters identified themselves as a physician, pharmacist, or a healthcare professional. The routes of suspected abuse were described in 15 reports as parenteral/intravenous/intramuscular (n=7), nasal/inhalation (n=4), oral/buccal (n=3), or transdermal (n=1).

The majority of the ketamine reports (28/39) reported one or more co-suspect drugs. These drugs included the Schedule 1 controlled substances, marijuana<sup>i</sup> (n=3), and heroin (n=2). The co-suspect drugs also included a substance that is not scheduled at the federal level, methoxetamine (n=1) – a dissociative hallucinogen, structurally similar to ketamine and phencyclidine (PCP), and other products from various drug classes. Of the remaining eleven reports listing ketamine as the only suspect drug, only one reported an outcome of death.

#### 4 DISCUSSION

Ketamine abuse has been reported for decades, and recent data indicate that it continues to occur, resulting in more than a hundred calls to poison control centers annually. Ketamine use also led to an estimated 669 ED visits in the U.S. in 2016-2017, with a large majority of cases being classified as abuse. National survey data indicate that ketamine abuse is relatively uncommon in the general population, with a lifetime prevalence of 1.3%, lower than other commonly abused hallucinogens, such as ecstasy and LSD (Acid). While still relatively low, lifetime ketamine abuse prevalence is highest in the 18-25 year old age group (1.8% in 2017), consistent with literature describing its use predominantly by older adolescents and young adults attending dance clubs and “raves.” Among 12<sup>th</sup> graders specifically, ketamine abuse is also relatively infrequent and has declined since 2000.

There were 35 ED cases involving abuse in the NEISS-CADES surveillance sample in 2016-2017 and 778 poison center exposure calls involving ketamine abuse or misuse (731 cases of abuse) in NPDS from 2013-2017. To help contextualize these numbers, we refer to recent FDA reviews describing abuse of propofol<sup>j</sup> (another anesthetic agent with abuse potential), buprenorphine<sup>k</sup>, and oxycodone<sup>l</sup>. The NEISS-CADES sample of EDs had no cases of propofol abuse and 751 cases of oxycodone non-medical use in 2016, and 287 cases of buprenorphine abuse in 2016-2017. NPDS contained 27 propofol and 3,233 buprenorphine abuse exposure calls from 2013-2017, 51,836 oxycodone abuse exposure calls from 2012-2016. These selected comparisons suggest that, not surprisingly, the public health burden of ketamine abuse is very low compared to that associated with prescription opioids.

When documented, the NPDS, NEISS-CADES, and FAERS data indicate that ketamine is abused via multiple routes—most commonly intranasal, ingestion/ oral, and injection (parenteral)—although the relative proportion of cases involving each of these routes varies by data source, and route is often unknown.

Clinical outcomes also varied by reporting system but, in general, suggest that ketamine abuse is infrequently associated with severe adverse outcomes, at least in the acute setting. A minority of the NEISS-CADES ED abuse visits resulted in hospitalization, even accounting for the three cases involving patients who left without being seen or against medical advice. Moderate health

---

<sup>i</sup> Reported as cannabis sativa subsp. indica top.

<sup>j</sup> Kang S. Propofol misuse and abuse. In DARRTS 07/27/2018, Ref ID 4298560.

<sup>k</sup> McAninch J. Epidemiology Review of Use, Misuse, and Abuse of Buprenorphine-Containing Products, and the Associations Between Depression, Pain, and Opioid Use Disorder. In DARRTS 12/21/2018, Ref ID 4361854.

<sup>l</sup> Mundkur M. Review of recent epidemiologic data on misuse and abuse of oxycodone. In DARRTS 5/21/2018, Ref ID 4295073

effects were the most commonly reported medical outcome among single-substance ketamine abuse and misuse exposure calls in NPDS, followed by minor effect, and there were no deaths identified among those cases. Reports of deaths and hospitalization were identified in FAERS in association with ketamine abuse, but only one report listed ketamine as the only suspected drug, and drug-event causal association has not been assessed for any of the FAERS cases.

Sales data from the previous FDA review are referenced in this review to provide insight into the magnitude of potential total use in the clinical setting and to provide context for the potential for diversion. Although sales data do not provide a direct measure of patient use, the amount of product purchased by various settings of care may be a possible surrogate for use if we assume the facilities purchase drugs in quantities reflective of actual patient use. Based on national sales distribution patterns of ketamine vials, the utilization appears to be largely in the hospital setting. Notably, sales to clinic settings more than doubled during 2013-2017, suggesting changes in utilization patterns. However, national data on diagnoses or indications directly linked with the administration of ketamine in the clinic or hospital settings were not available. We were not able to determine if the increasing sales are due to increases in off-label use, but literature suggests an increased interest in off-label use of ketamine. We were unable to assess off-label use as a source of diversion or abuse specifically. Despite increasing ketamine sales in recent years, and published literature suggesting growing interest in off-label therapeutic use of ketamine, the available trend data from NPDS and MTF do not suggest recent increases in ketamine abuse in the U.S. Rather, they suggest that ketamine abuse may even be declining. The U.S. DEA reports that most of the ketamine illegally distributed in the U.S. is diverted or stolen from sources such as veterinary clinics or smuggled into the U.S. from Mexico and then sold or shared among friends and acquaintances at parties or nightclubs,(8, 9) so it may be that increased use of ketamine in supervised medical settings has not translated to a corresponding growth in abuse.

### *Limitations of the Data*

To summarize the most recent reports from epidemiologic studies on ketamine abuse, we restricted our literature review to the most recent publications (2016-2017). As a result, we identified only a subset of the many published studies on ketamine abuse since its approval. Additionally, many of the observational studies that we identified were limited to specific population subgroups or populations outside of the U.S., where abuse patterns may differ from those in the U.S.

Although NSDUH and MTF are capable of producing national estimates of drug misuse and abuse, they are subject to the inherent limitations of self-reported data, such as non-response bias, misclassification, and recall bias. Additionally, individuals with advanced substance use disorders may be underrepresented, particularly if they become homeless, incarcerated, or enter a residential treatment facility.

NPDS captures exposure events that are called in by someone asking for help with the exposure (public or healthcare professional), and information is limited to what is provided by the caller. These calls likely represent a small proportion of exposure events and are not likely to be representative of all abuse exposures, but it is informative for characterizing the public health burden of acute harms from ketamine abuse. AAPCC cautions that “data referenced from

AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s)” (AAPCC Data Policies, October 2015). In particular, unwitnessed out-of-hospital deaths due to drug overdoses are unlikely to generate a call to poison control centers.

We did not include NEISS-CADES data prior to 2016 because abuse related ED visits were not previously captured in this database. NEISS-CADES data include reports from approximately 60 hospitals throughout the United States and are nationally representative. However, the data may be limited by low sensitivity; NEISS-CADES reports an overall sensitivity of 33% but this varies by type of adverse drug event (NEISS-CADES user’s manual, 2017).

We included FAERS data from a previous review by DPV II<sup>m</sup> to add to our understanding of ketamine abuse and the nature of adverse events associated with this abuse. The FAERS assessment is a high-level overview of the reports in the database received from January 2015 to September 11, 2017. As such, individual cases have not been reviewed; therefore, the data may contain duplicates, and drug-event causal association has not been assessed. As part of the sponsor’s pharmacovigilance regulatory requirements, they are required to monitor and report medical literature case reports. The FAERS database contains case reports from the NPDS database through the published American Association of Poison Control Centers annual reports; thus, there may be overlap in the data presented in the FAERS and NPDS sections of this review.

The FAERS database is a passive reporting system and has a number of limitations, including under-reporting. In particular, cases of drug abuse are likely under reported to FAERS because people who abuse drugs are unlikely to report, as supported by the relatively low number of consumer reports received for ketamine. Missing data from these systems, and the potential for misclassification (e.g., of abuse as non-abuse) are two limitations common to both FAERS and NPDS. This hinders our ability to provide comprehensive characteristics of patients abusing these drugs, and may lead to underestimates of the true public health burden caused by the abuse of these drugs. Given the spontaneous nature of adverse event reports and limitations described, these data cannot be used to inform the rate of abuse.

## 5 CONCLUSIONS

The risks of abuse and associated harms are important considerations in determining appropriate risk mitigation strategies and postmarket surveillance for esketamine, if approved. Ketamine abuse has been recognized for decades, and it is classified as a Schedule III drug under the Controlled Substances Act. In recent years, there have been numerous cases of ketamine abuse resulting in adverse events or the need for medical attention or advice; however, most of these cases resulted in minor or moderate adverse effects and did not require hospitalization. National surveys indicate a low prevalence of ketamine use in the general population and in high school students, consistent with literature suggesting that ketamine abuse is concentrated in smaller population subgroups such as older adolescents and young adults participating in “rave” or nightclub scenes. We did not observe increasing trends in ketamine abuse calls to poison centers or in self-reported abuse despite contemporaneous increasing sales and expanding off-label use of ketamine. According to DEA reports, much of the illegally distributed ketamine in the U.S. is smuggled in from other countries or diverted from veterinary sources, and the evidence is

---

<sup>m</sup> Patel C. Abuse-related data for WHO questionnaire. In DARRTS 10/2/2017, Ref ID 4161583.

insufficient to know whether the distribution and use of pharmaceutical ketamine in humans contribute substantially to ketamine abuse in the U.S.

APPEARS THIS WAY ON ORIGINAL

APPENDICES

APPENDIX A. NPDS DEFINITIONS OF EXPOSURE REASONS

<b>NPDS Definitions for Intentional Exposure Reason Categories from the NPDS Data Dictionary</b>		
<b>Intentional Exposure Reasons</b>	<b>NPDS Definition</b>	<b>Case Inclusions/ Exclusions examples</b>
<b>Suspected Suicides</b>	“An exposure resulting in the inappropriate use of a substance for self-harm or self-destruction or manipulative reasons.”	<p>“Case Inclusions: Suicides, suicide attempts, and suicide gestures, whether suspected or confirmed</p> <ul style="list-style-type: none"> <li>• Cases in which history indicates patient was upset or depressed</li> <li>• Patients who provide explanations for their actions such as "arguing with parents," "disturbed about poor grades," or "having marital problems"</li> <li>• Ingestions of large quantities of one or more drugs where the only likely explanation is the patient's intent to harm himself”</li> </ul>
<b>Abuse</b>	“An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect”, including recreational use of a substance for any effect.	<p>“Case Inclusions:</p> <p>A person who inhales helium to talk funny</p> <ul style="list-style-type: none"> <li>• A person who uses GHB at a dance club</li> <li>• An infant with toxic effects or withdrawal symptoms as a result of the mother’s drug abuse while the child was in utero or while breast-feeding”</li> </ul>
<b>Misuse</b>	“An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.”	<p>“Case Inclusions:</p> <p>A person deliberately mixes or applies a pesticide inappropriately so it will be more effective</p> <ul style="list-style-type: none"> <li>• A person deliberately increases the dosage of a medication to enhance its therapeutic effect</li> <li>• Overuse of caffeine to study for an exam</li> </ul> <p>Case Exclusions:</p> <p>Patients who want to get high (should be INTENTIONAL ABUSE)</p> <ul style="list-style-type: none"> <li>• Suspected child abuse (should be OTHER-MALICIOUS)”</li> </ul>
<b>Unknown</b>	Exposures that are deemed to be intentional although the specific motive is undetermined.	N/A

**APPENDIX B. NPDS DEFINITION FOR MEDICAL OUTCOME**

<b>NPDS Definitions for Medical Outcome from the NPDS Data Dictionary</b>	
<b>Medical Outcome</b>	<b>NPDS Definition</b>
<b>No Effect</b>	“The patient developed no symptoms (clinical effects) as a result of the exposure. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that the poison center is reasonably certain no effects will occur.”
<b>Minor Effect</b>	“The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not worsen. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.”
<b>Moderate Effect</b>	“The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.”
<b>Major Effect</b>	“The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the symptoms are anticipated to be long-term or permanent.”

**APPENDIX C. NPDS GENERIC AND PRODUCT CODES**

NPDS Generic and Product Codes Use for NPDS Data Extraction		
	Generic Code	Product Code
Ketamine		(b) (4)
Note: These product codes must be redacted for public release		

**APPENDIX D. NEISS-CADES DEFINITIONS OF ADVERSE DRUG EVENTS**

<b>NEISS-CADES Definitions for Definitions of Case Type from NEISS-CADES Data Dictionary</b>		
<b>Analytic Category</b>		<b>NEISS-CADES Definition</b>
<b>Nonmedical Use</b>	<b>ABUSE</b>	Clinician diagnosis of abuse (for current ED visits) or documentation of recreational use (e.g., “to get high”, “at a party”, “crushing and snorting”, “bought off street”)
	<b>UNKNOWN INTENT</b>	Clinician diagnosis of undetermined intent or insufficient documentation to categorize the case as abuse, therapeutic, self-harm/suicide, or assault. Also used for cases with conflicting information about intent without a clarifying clinician diagnosis.
	<b>THERAPEUTIC MISUSE</b>	Documentation of therapeutic intent, but the pharmaceutical was intentionally not used as directed OR case details call the therapeutic intent into question (e.g., taking someone else’s prescription medication for pain, intentionally taking a very large dose with a stated therapeutic purpose)
<b>UNSUPERVISED PEDIATRIC EXPOSURE</b>		Access of a medication by a child aged <11 years without caregiver permission or oversight. Most cases involve ingestions or suspected ingestions.
<b>THERAPEUTIC USE</b>		Adverse events following drugs used for therapeutic intent with no indication of misuse. Includes adverse effects, allergic reactions, supratherapeutic effects, medication errors, vaccine reactions, and secondary effects (e.g., choking on a pill)
<b>SELF-HARM/SUICIDE</b>		Clinician diagnosis of self-harm or suicide attempt or documented intent to kill or injure oneself using pharmaceuticals
<b>ASSAULT</b>		Deliberate intent to cause harm to another individual with a pharmaceutical product

## **APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**

### **FDA Adverse Event Reporting System (FAERS)**

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

## 7 REFERENCES

1. Ketalar (ketamine hydrochloride) [package insert]. Chestnut Ridge, NY: Par Pharmaceutical; April 2017. Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016812>.
2. Berman RM, Capiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant Effects of Ketamine in Depressed Patients. *Biol Psychiatry*. 2000;47:351-4.
3. Hocking G, Cousins MJ. Ketamine in Chronic Pain Management: An Evidence-Based Review. *Anesthesia & Analgesia*. 2003;97(6):1730-9.
4. Zarate CA, Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of general psychiatry*. 2006;63(8):856-64.
5. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain*. 2009;147(1-3):107-15.
6. Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous MS, Marinus J, Sarton EY, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain*. 2009;145(3):304-11.
7. Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. *JAMA Psychiatry*. 2017;74(4):399-405.
8. Drug Enforcement Administration. U.S. Department of Justice. Drugs of Abuse: A DEA resource guide. 2017 edition. [https://www.dea.gov/sites/default/files/drug\\_of\\_abuse.pdf](https://www.dea.gov/sites/default/files/drug_of_abuse.pdf)
9. Drug Enforcement Administration (DEA). Office of Diversion Control, Drug & Chemical Evaluation Section. Ketamine; August 2013. [https://www.deadiversion.usdoj.gov/drug\\_chem\\_info/ketamine.pdf](https://www.deadiversion.usdoj.gov/drug_chem_info/ketamine.pdf)
10. Food and Drug Administration [Internet]. "Assessment of Abuse Potential of Drugs: Guidance for Industry" [updated 2017 Jan; cited 02Jan2019] Available from: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>.
11. Food and Drug Administration [Internet]. "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: Guidance for Industry" [updated 2017 Nov.; cited 02 Jan 2019] Available from: <https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf>.
12. Substance Abuse and Mental Health Administration. (2018). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health*. (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from <https://www.samhsa.gov/data/>

13. Center for Behavioral Health Services and Quality. (2018). *2017 National Survey on Drug Use and Health: Detailed Tables*. Rockville, MD
14. MTF 2018: Johnston L.D., Miech, R.A., O'Malley, P.M., Bachman, J.G., Schulenberg, J.E. & Patrick, M.E. *Monitoring the Future national survey results on drug use: 1975-2017: Overview, key findings on adolescent drug use*. Ann Arbor: Institute for Social Research, The University of Michigan.
15. Miech R, Johnston L.D., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Patrick, M. E. (2018). *Monitoring the Future national survey results on drug use, 1975–2017: Volume I, Secondary school students*. Ann Arbor: Institute for Social Research, The University of Michigan. Available at <http://monitoringthefuture.org/pubs.html#monographs>.
16. American Association of Poison Control Centers [Internet] "National Poison Data System" [cited 31 October 2018]. Available from <http://www.aapcc.org/data-system>.
17. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. *Clinical Toxicology (Phila)*. 2018 Dec 21;:1-203. PubMed PMID:30576252.
18. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *Jama*. 2016;316(20):2115-25.
19. Jhung MA, Budnitz DS, Mendelsohn AB, Weidenbach KN, Nelson TD, Pollock DA. Evaluation and overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES). *Medical care*. 2007;45(10 Supl 2):S96-102.
20. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *Jama*. 2006;296(15):1858-66.
21. Schroeder TJ, Ault K. National Electronic Injury Surveillance System (NEISS) sample design and implementation from 1997 to present. Washington, DC: US Consumer Products Safety Commission; 2001. Available at: <http://www.cpsc.gov/neiss/2001d011-6b6.pdf>
22. Sassano-Higgins S, Baron D, Juarez G, Esmaili N, Gold M. A REVIEW OF KETAMINE ABUSE AND DIVERSION. *Depression and anxiety*. 2016;33(8):718-27.
23. Liu Y, Lin D, Wu B, Zhou W. Ketamine abuse potential and use disorder. *Brain research bulletin*. 2016;126(Pt 1):68-73.
24. Bokor G, Anderson PD. Ketamine: an update on its abuse. *J Pharm Pract*. 2014;27(6):582-6.
25. Wolff K, Hay AW, Sherlock K, Conner M. Contents of "Ecstasy". *Lancet*. 1995;346:1100-1.

26. Hong YL, Yee CH, Tam YH, Wong JH, Lai PT, Ng CF. Management of complications of ketamine abuse: 10 years' experience in Hong Kong. *Hong Kong medical journal = Xianggang yi xue za zhi*. 2018;24(2):175-81.
27. Yang SS, Jang MY, Lee KH, Hsu WT, Chen YC, Chen WS, et al. Sexual and bladder dysfunction in male ketamine abusers: A large-scale questionnaire study. *PloS one*. 2018;13(11):e0207927.
28. Palamar JJ, Acosta P, Sherman S, Ompad DC, Cleland CM. Self-reported use of novel psychoactive substances among attendees of electronic dance music venues. *The American journal of drug and alcohol abuse*. 2016;42(6):624-32.
29. Jin F, Hammoud MA, Maher L, Degenhardt L, Bourne A, Lea T, et al. Age-related prevalence and twelve-month incidence of illicit drug use in a cohort of Australian gay and bisexual men: Results from the Flux Study. *Drug and alcohol dependence*. 2018;188:175-9.
30. Palamar JJ, Mauro PM, Han BH, Martins SS. Shifting characteristics of ecstasy users ages 12-34 in the United States, 2007-2014. *Drug and alcohol dependence*. 2017;181:20-4.
31. Deimel D, Stover H, Hosselbarth S, Dichtl A, Graf N, Gebhardt V. Drug use and health behaviour among German men who have sex with men: Results of a qualitative, multi-centre study. *Harm reduction journal*. 2016;13(1):36.
32. Schmidt AJ, Bourne A, Weatherburn P, Reid D, Marcus U, Hickson F. Illicit drug use among gay and bisexual men in 44 cities: Findings from the European MSM Internet Survey (EMIS). *The International journal on drug policy*. 2016;38:4-12.
33. Feng LY, Yu WJ, Chang WT, Han E, Chung H, Li JH. Comparison of illegal drug use pattern in Taiwan and Korea from 2006 to 2014. *Substance abuse treatment, prevention, and policy*. 2016;11(1):34.

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

AMY E SEITZ  
02/14/2019 04:02:38 PM

ROSE G RADIN  
02/14/2019 04:22:28 PM

JANA K MCANINCH  
02/14/2019 09:45:32 PM

## Clinical Inspection Summary

<b>Date</b>	February 13, 2019
<b>From</b>	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
<b>To</b>	Hiren Patel, Pharm.D., Regulatory Project Manager Jean Kim, M.D., Clinical Reviewer Bernard Fischer, M.D., Clinical Team Leader Division of Psychiatry Products (DPP)
<b>NDA #</b>	211243
<b>Applicant</b>	Janssen Pharmaceuticals, Inc.
<b>Drug</b>	Esketamine
<b>NME</b>	No
<b>Therapeutic Classification</b>	Glutamate Receptor Modulator
<b>Proposed Indication</b>	Adjunctive Antidepressant for Treatment Resistant Depression
<b>Consultation Request Date</b>	10/15/2018
<b>Summary Goal Date</b>	02/14/2019
<b>Action Goal Date</b>	03/04/2019
<b>PDUFA Date</b>	03/04/2019

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor Janssen Pharmaceuticals, Inc., the Clinical Research Organization (CRO) (b) (4) and eight clinical investigator (CI) sites (Drs. Hatti, Ravindran, Bermak, Janu, Montejo, Trivedi, Nadjafi, and Cubala) were inspected in support of this NDA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The preliminary compliance classification of the inspections of the sponsor Janssen and the Clinical Research Organization (CRO) (b) (4), and the final compliance classification of the inspections of Drs. Hatti, Bermak, Janu, Montejo, Nadjafi is No Action Indicated (NAI). The preliminary compliance classifications of the inspections of Drs. Arun, Trivedi, and Cubala is VAI.

### II. BACKGROUND

Esketamine hydrochloride, a glutamate receptor modulator, is a Schedule III controlled substance under the Controlled Substances Act. The sponsor has developed a nasal spray formulation of esketamine for treatment-resistant depression, which is defined as major depressive disorder (MDD) in adults who do not have clinically meaningful improvement after treatment with at least two different antidepressants prescribed in adequate dosages for adequate duration (at least six weeks) in the current episode of depression. FDA granted the esketamine development program for treatment-resistant depression Fast Track designation on July 26, 2012 and Breakthrough Therapy designation on November 7, 2013.

The following three protocols were inspected in support of this application:

**Protocol ESKETINTRD3001**, “A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fixed Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression”

This study took place in 42 sites in the United States, 9 sites each in France, Belgium, and Mexico, 8 sites in Brazil, 5 sites each in Canada and Slovakia, 3 sites in Hungary, and 2 sites in Estonia beginning September 3, 2015 and February 20, 2018. A total of 346 subjects were enrolled in the study.

This was a 4-week randomized, double-blind, active-controlled study to evaluate the efficacy, safety, and tolerability of fixed doses of intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]), compared with a newly initiated oral antidepressant (active comparator) plus intranasal placebo, in adult subjects with treatment-resistant depression.

The primary efficacy endpoint was the change in the Montgomery and Asberg Depression Rating Scale (MADRS) total score from baseline (Day 1 prior to randomization) to the end of the 4-week double-blind induction phase. The first key secondary endpoint was the proportion of subjects showing onset of clinical response by Day 2 that was maintained through the end of the 4-week double-blind induction phase. The second and third key secondary endpoints were the change from baseline to the end of the 4-week double-blind induction phase in Sheehan Disability Scale (SDS) and the Patient Health Questionnaire (PHQ-9) total score, respectively.

**Protocol ESKETINTRD3002**, “A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects with Treatment-resistant Depression”

This study took place in 6 sites in the Czech Republic, 9 sites in Germany, 7 sites in Poland, 7 sites in Spain, and 10 sites in the United States beginning August 07, 2015 and ending November 06, 2017. A total of 227 subjects were enrolled in the study. This study had the same design as Protocol ESKETINTRD3001 except it was a flexible dose study.

**Protocol ESKETINTRD3003**, “A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression”

This study took place in 4 sites in Belgium, 13 sites in Brazil, 2 sites in Canada, 11 sites in the Czech Republic, 1 site in Estonia, 5 sites in France, 4 sites in Germany, 12 sites in Hungary, 4 sites in Italy, 6 sites in Mexico, 15 sites in Poland, 3 sites in Slovakia, 10 sites in Spain, 4 sites in Sweden, 16 sites in Turkey, and 54 sites in the United States beginning 06 October 2015 and 15 February 2018. A total of 705 subjects were enrolled.

This was a randomized, double-blind, relapse prevention study in adults with treatment resistant depression who had achieved stable remission or stable response after an induction and optimization course of treatment with intranasal esketamine + oral antidepressant. The primary efficacy endpoint was the time from subject randomization to the first documentation (earliest date) of a relapse in the maintenance phase.

### **Rationale for Clinical Investigator Site Selection**

Dr. Hatti's site was selected because the data from his site impacted the overall efficacy results of the study. Performing a sensitivity analysis by removing the data from this site modified the primary efficacy result (from statistically significant to not statistically significant). Dr. Hatti does not have prior inspection history.

Dr. Ravindran's site was selected because the data from his site impacted the overall efficacy results of the study. Performing a sensitivity analysis by removing the data from this site modified the primary efficacy result (from statistically significant to not statistically significant). He has a relatively high enrollment in Study ESKETINTRD3001 and no prior inspection history.

Dr. Bermak's site was selected because the data from his site impacted the overall efficacy results of the study. Performing a sensitivity analysis by removing the data from this site modified the primary efficacy result (from statistically significant to not statistically significant). His last inspection was May 2016 (NAI).

Dr. Janu's site was selected because the data from his site impacted the overall efficacy results of the study. Performing a sensitivity analysis by removing the data from this site modified the primary efficacy result (from statistically significant to not statistically significant). He has a relatively high enrollment in ESKETINTRD3002 and no prior inspection history.

Dr. Montejo's site was selected because the data from his site impacted the overall efficacy results of the study. Performing a sensitivity analysis by removing the data from this site modified the primary efficacy result (from statistically significant to not statistically significant). He has no prior inspection history.

Dr. Trivedi's site was selected because the data from his site impacted the overall efficacy results of the study. Performing a sensitivity analysis by removing the data from this site modified the primary efficacy result (from statistically significant to not statistically significant). He has no prior inspection history.

Dr. Nadjafi's site was selected because of relatively high enrollment in Study ESKETINTRD3003. He has no prior inspection history.

Dr. Cubala's site was selected because the data from his site impacted the overall efficacy results of the study. Performing a sensitivity analysis by removing the data from this site modified the primary efficacy result (from statistically significant to not statistically significant). He has high enrollment and no prior inspection history.

### **Rationale for the Inspection of sponsor and CRO (b) (4)**

Inspection of the sponsor is warranted to ensure that there is no data integrity or subject protection or other Good Clinical Practice (GCP) concerns with the studies and the data submitted for this application.

Inspection of CRO (b) (4) is warranted to ensure that there are no concerns with the safety data submitted for this application. The sponsor transferred contractual responsibility for medical safety monitoring to (b) (4) for all three pivotal studies.

**III. RESULTS (by site):**

<b>Site #/ Name of CI Address</b>	<b>Protocol #/ # of Enrolled Subjects</b>	<b>Inspection Dates</b>	<b>Classification</b>
Site # US10011 <b>Shivkumar Hatti, M.D.</b> 107 Chesley Drive Suite 4 Media, PA 19063	ESKETINTRD 3001 Subjects: 10	December 12- 14, 17, 2018	NAI
Site #CA10004 <b>Arun Ravindran, Ph.D.</b> 100 Stokes Street Toronto, Ontario, M6J 1H4 Canada	ESKETINTRD 3001 Subjects: 12	January 07-11, 2019	VAI*
Site #US10001 <b>Jason Bermak, M.D.</b> 1330 Lincoln Avenue San Rafael, CA 94901	ESKETINTRD 3002 Subjects: 6	December 10- 13, 2018	NAI
Site #CZ10018 <b>Janu Lubos, M.D.</b> Smrkova 23 Plzen, NA 31200 Czech Republic	ESKETINTRD 3002 Subjects: 13	December 10- 14, 2018	NAI
Site #ES10004 <b>Angel L. Montejo, M.D., Ph.D.</b> <b>(Juan Matias Fernandez)</b> Av. Comuneros, 27 Salamanca, NA 37003, Spain	ESKETINTRD 3002 Subjects: 4	December 17- 19, 2018	NAI
Site #US10060 <b>Madhukar Trivedi, M.D.</b> 6363 Forest Park Rd, Dallas, TX 75235	ESKETINTRD 3002 Subjects: 10	January 07-11, 2019	VAI*
Site #US10044 <b>Morteza Nadjafi, M.D.</b> 721 N. Magnolia Ave Orlando, FL 32803	ESKETINTRD 3003 Subjects: 12 enrolled	December 7, 10-13, 2018	NAI
Site #PL10003 <b>Wieslaw Cubala, M.D., Ph.D.</b> Uniwersyteckie Centrum Kliniczne Klinika, Chorob Psychicznych i Zaburzen, Nerwicowych Debinki 7, Gdansk, NA 80- 952 Poland	ESKETINTRD 3003 Subjects: 44 (44 enrolled)	January 14-18, 2019	VAI*

NDA #211243 Clinical Inspection Summary (CIS)

<b>Janssen Research &amp; Development, LLC</b> 1125 Trenton-Harbourton Road Titusville, NJ 08560	ESKETINTRD 3001 3002 3003	January 22-25, 28-30, February 4, 7, 2019	NAI*
(b) (4)	ESKETINTRD 3001 3002 3003	(b) (4)	NAI*

Key to Compliance Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable

\* = Preliminary classification based on information in 483 or preliminary communication with the field; the final EIR has not been received from the field and/or the complete review of final EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

**1. Shivkumar Hatti, M.D.**

At this site for Protocol ESKETINTRD3001, 14 subjects were screened, 10 were enrolled, and 9 subjects completed the study. One subject (# (b) (6)) was terminated early due to manic symptoms.

The records for all 14 screened subjects were reviewed. The study and subject specific records reviewed during this inspection included, but were not limited to, subject informed consent forms, monitoring logs, delegation logs, enrollment logs, Institutional Review Board (IRB) correspondence and approvals, sponsor/monitor correspondence, investigator's agreement, device accountability records, and source documentation including the primary and the key secondary efficacy endpoint data.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

**2. Arun Ravindran, Ph.D.**

At this site for Protocol ESKETINTRD3001, 24 subjects were screened, 12 were enrolled, and 11 subjects completed the study. One subject withdrew consent.

The study and subject specific records reviewed during this inspection included, but were not limited to, protocol amendments, signed investigator agreement, financial disclosure statement, all regulatory study related records and IRB/sponsor correspondence, sponsor monitoring activities, informed consents, subject study eligibility, adverse event reporting, the primary and the key secondary efficacy endpoint source documents, and concomitant medications.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection, including the following findings:

An investigation was not conducted in accordance with the signed statement of the investigator and investigational plan. Specifically, Subject # [REDACTED] (b) (6) and Subject # [REDACTED] (b) (6) were not eligible for Study ESKETINRD3001 as they each met exclusion criteria related to prohibited concomitant therapy prior to dosing with investigational product:

- A. Subject # [REDACTED] (b) (6) (in esketamine 56 mg group) suffered from extreme anticipatory anxiety which resulted in elevated heart rate prior to study treatment. The subject was pre-treated with lorazepam prior to each nasal dose of esketamine 56 mg.
- B. Subject [REDACTED] (b) (6) (in esketamine 56 mg group) was receiving trazodone 50 mg treatment for insomnia for several years prior to study enrollment. The subject did not discontinue trazodone before Day 1 of the double-blind induction phase of the study.

Dr. Ravindran adequately responded to the inspection findings in a letter dated January 25, 2019.

*Reviewer's comment: These protocol deviations were reported to FDA.*

### **3. Jason Bermak, M.D.**

At this site for Protocol ESKETINTRD3002, 11 subjects were screened, and 6 were enrolled and completed the study. The study and subject specific records reviewed during this inspection included protocol amendments, signed investigator agreement, financial disclosure statement, all regulatory study related records and IRB/sponsor correspondence, all sponsor monitoring activities, training documentation for electronic systems, all informed consents, enrolled subjects source documents including subject study eligibility, medical history, blinding/randomization procedures, adverse event reporting, the primary and the key secondary efficacy endpoint source documents, and the concomitant medications.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

### **4. Janu Lubos, M.D.**

At this site for Protocol ESKETINTRD3002, 23 subjects were screened, 14 enrolled, and 13 subjects completed the study. One subject withdraw consent prior to dosing.

The records reviewed included protocol amendments, signed investigator agreement, financial disclosure statement, delegation of authority, firm's training program, the IRB membership roster and all IRB approval letters, all monitor visit reports from 08/06/2015 to 02/16/2018, all informed consents, electronic data capture (EDC) training documentation, randomization schedule and test article exposure and dosing information, subject study eligibility including study screening documentation such as psychiatric histories, medical histories, concomitant medications and physical exams; adverse event reporting, and all primary and the key secondary efficacy endpoint data.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

**5. Angel L. Montejo, M.D., Ph.D. (Juan Matias Fernandez)**

Dr. Fernandez transferred the PI responsibility to Dr. Montejo prior to the study beginning. At this site for Protocol ESKETINTRD3002, 8 subjects were screened, and 4 were enrolled and completed the study.

The study and subject specific records for all subjects were reviewed during this inspection including informed consent forms, randomization schedule and test article exposure and dosing information, confirmation of study subject identification and demographics, study screening documentation including physical exams, psychiatric histories, medical histories, and concomitant medications, as they relate to inclusion and exclusion criteria, results from follow-up visits including primary (MADRS scores) and secondary (SDS & PHQ-9) efficacy endpoint data. The inspection also reviewed the equipment calibration records, clinical standard operating procedures, correspondence between the site, ethics committee, & sponsor, investigational product receipt, storage, distribution, and retention records, temperature logs for investigational product storage, facility layout and capacities.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

**6. Madhukar Trivedi, M.D.**

At this site for Protocol ESKETINTRD3002, 21 subjects were screened, and 10 were enrolled and randomized. Nine subjects completed the study. One subject discontinued because the subject could no longer make appointments.

The study and subject specific records for all 10 enrolled subjects were reviewed during this inspection including, but not limited to, protocol amendments, signed investigator agreement, financial disclosure statement, all regulatory study related records and IRB/sponsor correspondence, sponsor monitoring activities, informed consents, subject study eligibility, adverse event reporting, the primary and the key secondary efficacy endpoint source documents, and concomitant medications.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection, including the following findings:

- A. Failure to maintain raw study data and audit trails for several key secondary endpoints including certain clinician-completed evaluations and patient reported outcomes (e.g., PAQ; PHQ-9; SDS; GAD-7; EQ-5D-5L) that were purportedly recorded through site pads for 15 out of 21 subjects (# (b) (6) through # (b) (6) and # (b) (6)); 8 of these subjects were enrolled into the study. An additional CD provided during the inspection on January 11, 2019 was also incomplete and missing the above-mentioned data for the same subjects.
- B. An investigation was not conducted in accordance with the investigational plan. Specifically, a 1-hour post-dose EKG was not completed as per protocol at the study Visit 2.4/Day 8 for Subject # (b) (6).

Dr. Trivedi adequately responded to the inspection findings in a letter dated January 17, 2019. The missing key secondary endpoint data in CDs were made available to FDA inspectors later in the inspection. Also, Dr. Trivedi investigated and found that the 1-hour post-dose EKG for Subject # (b) (6) at the Study Visit 2.4/Day 8 was completed. Because the EKG machine used was not updated to daylight savings time, the stamping time of the EKG was one hour earlier (09:21 instead of 10:21 after the dosing at 09:25) which made EKG appear to be completed before dosing.

#### **7. Morteza Nadjafi, M.D.**

At this site for Protocol ESKETINTRD3003, 17 subjects were screened, 12 enrolled, and 9 were randomized into the double-blind maintenance phase. Three subjects withdrew consent.

A complete review of all 17 screened subject records was conducted including the informed consent forms, the subject medical records (progress notes, physical exams, lab results, primary and secondary efficacy data, adverse events, etc.), subject worksheets, monitoring visits, correspondence between Dr. Nadjafi and the IRB, case report forms, test article accountability, training documentation, firm's history, and administrative documents.

The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events

#### **8. Wieslaw Cubala, M.D.**

At this site for Protocol ESKETINTRD3003, 78 subjects were screened, 44 enrolled, and 25 were randomized in the double-blind treatment phase. Subject # (b) (6) discontinued due to the adverse events of dizziness and numbness. Subjects # (b) (6) discontinued due to the adverse events of elevated ALT. Subject # (b) (6) withdrew consent.

A complete review of 20 subject records was conducted. The study and subject specific records reviewed during this inspection included, but were not limited to, protocol amendments, signed investigator agreement, financial disclosure statement, all regulatory study related records and IRB/sponsor correspondence, informed consents, adverse event reporting, the primary efficacy endpoint data, and concomitant medications.

The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection, including the following finding:

An investigation was not conducted in accordance with the investigational plan. Specifically,

- A. Subjects were under-dosed with the Investigational Product (IP) in part due to the clinical investigator's failure to oversee the proper dispensing of the intranasal esketamine as required by the protocol during the scheduled study visits. The under-dosing was not recognized and captured in the original source documents at the time of the IP administration. Specifically,
  - Subject # (b) (6) received a partial dose of Kit #137908 on January 13, 2017

## NDA #211243 Clinical Inspection Summary (CIS)

- Subject # [REDACTED] (b) (6) received a partial dose of Kit #278990 on January 10, 2017 and received a partial dose of Kit #279011 and #279112 on January 17, 2017
- Subject # [REDACTED] (b) (6) received a partial dose of Kit # 279009 on January 16, 2017
- Subject # [REDACTED] (b) (6) received a partial dose of Kit #279303 on February 22, 2017, partial doses of Kits #279333 and #279334 on February 27, 2017, and a partial dose of Kit #791248 on March 03, 2017
- Subject # [REDACTED] (b) (6) received a partial dose of Kit #745967 on August 16, 2017.

- B. Subjects were administered IP from the incorrect test kit/device. For example, Subject # [REDACTED] (b) (6) was assigned Kit #279012 but was dispensed Kit #279112 on January 17, 2017.

Dr. Cubala adequately responded to the inspection findings in a letter dated February 8, 2019.

*Reviewer's comment: These protocol deviations were reported to FDA. The sponsor has addressed the device malfunction issue and reported it in the clinical study report. Due to the low percentage of subjects affected by the device malfunction, the overall study efficacy results are unlikely to be affected. Also, since device malfunction only caused low dosing, patient safety is not expected to be affected.*

## 9. Sponsor

The FDA field investigator, together with two subject matter experts (SMEs) from CDER/OSI, reviewed the following for this sponsor inspection: 1572 and financial disclosure, selection and monitoring of clinical investigators; vendor list, the contracts and transfers of regulatory obligations, management of the vendors, data collection, handling, and management including database lock and unlock dates and reasons; protocol deviations, electronic data capture and data systems; quality control; safety and adverse event reporting; the sponsor's oversight plan, and site monitoring visit reports. The inspection also investigated the complaints of partial dosing due to device malfunction. The sponsor addressed the partial dosing issues and reported in the clinical study report. The sponsor subsequently developed a new commercial device. In summary, the sponsor inspection did not reveal significant regulatory violations.

## 10. [REDACTED] (b) (4)

The FDA field investigator, together with the subject matter expert (SME) from CDER/OSI, conducted the inspection for [REDACTED] (b) (4) for medical safety monitoring. No significant regulatory violations were noted.

*{See appended electronic signature page}*

Jenn W. Sellers, M.D., Ph.D.  
Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan D. Thompson, M.D. for  
Phillip Kronstein, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**cc:**

Central Doc. Rm. NDA #211243  
DPP /Project Manager/Hiren Patel  
DPP/Division Director (Acting)/Tiffany Farchione  
DPP/Medical Officer/Jean Kim  
DPP/Clinical Team Leader/Bernard Fischer  
OSI/Office Director/David Burrow  
OSI/DCCE/Division Director/Ni Khin  
OSI/DCCE/Branch Chief/Kassa Ayalew  
OSI/DCCE/Team Leader/Phillip Kronstein  
OSI/DCCE/Team Leader/Susan Thompson  
OSI/DCCE/GCP Reviewer/Jenn Sellers  
OSI/GCP Program Analyst/Yolanda Patague

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

JENN W SELLERS  
02/13/2019 07:27:39 AM

SUSAN D THOMPSON  
02/13/2019 08:56:34 AM

KASSA AYALEW  
02/13/2019 09:03:09 AM



**Consult Question:** “Review of the FPI for PLLR compliance.”

## INTRODUCTION AND BACKGROUND

On September 4, 2018, the applicant, Janssen Pharmaceuticals, Inc., submitted an original 505(b)(1) New Drug Application (NDA) for SPRAVATO (esketamine), NDA 211243, for the treatment of treatment resistant depression. DPP consulted DPMH on September 4, 2018, to assist with the Pregnancy and Lactation subsections of labeling.

- SPRAVATO (esketamine) was granted Fast Track designation on July 26, 2012, and Breakthrough Therapy designation on November 7, 2013.

### SPRAVATO (esketamine)<sup>2</sup>

Dosage and Administration	<ul style="list-style-type: none"><li>• Should be administered in conjunction with an oral antidepressant</li><li>• Induction Phase (weeks 1 to 4): two treatment sessions per week<ul style="list-style-type: none"><li>○ Starting Day 1 dose: 56 mg</li><li>○ Subsequent doses: 56mg or 84mg daily</li></ul></li><li>• Maintenance Phase<ul style="list-style-type: none"><li>○ Weeks 5 to 8: 56 mg or 84 mg weekly</li><li>○ From Week 9: 56 mg or 84 mg every two weeks or once weekly</li></ul></li></ul>
Drug Class	Glutamate receptor modulator
Mechanism of action	It is a non-competitive, subtype non-selective, activity-dependent glutamate receptor modulator
Molecular weight	274.3 Daltons
Half-life	Terminal half-life ranged from 7-12 hours
Protein Binding	43-45% protein bound
Bioavailability	Mean absolute bioavailability ~48%
Serious Adverse Reactions	<ul style="list-style-type: none"><li>• There is a boxed warning for suicidal thoughts and behaviors</li><li>• Patients with unstable or poorly controlled hypertension may be at increased risk of adverse cardiovascular or cerebrovascular effects.</li><li>• May impair attention, judgement, thinking, reaction speed and motor skills. Use caution when operating machinery.</li></ul>

## REVIEW

### ***PREGNANCY***

#### Treatment-resistant Major Depressive Disorder (MDD)in Pregnancy<sup>3</sup>

<sup>2</sup> SPRAVATO (esketamine) proposed package insert

<sup>3</sup> DESYREL (trazodone) NDA 18207, Catherine Roca, M.D., May 24, 2018. DARRTS Reference ID 4268512

- Treatment-resistant depression is commonly defined as major depressive disorder that has not responded adequately to two trials of antidepressant treatment of adequate dose and duration.<sup>4</sup>
- Approximately 30% of patients with MDD are considered to be treatment resistant.<sup>5</sup>
- Current strategies for treating treatment-resistant depression include augmentation of antidepressant therapy with other medications (e.g., atypical antipsychotics, lithium, etc.), as well as use of somatic therapies, such as electroconvulsive therapy (ECT).<sup>6</sup>
- The reader is referred to the DPMH review of DESYREL (trazodone) by Catherine Roca, M.D., for a review of the literature on major depressive disorder and pregnancy outcomes. The literature on major depressive disorder described in the DESYREL review was independently considered for this review.

### Nonclinical Experience

Ketamine administered intravenously at anesthetic dose levels to female rats in the second trimester of pregnancy caused neuronal changes in their offspring which showed behavioral changes and impaired memory up to young adult age. When female monkeys were treated intravenously with ketamine at anesthetic dose levels in the third trimester of pregnancy, neuronal cell death was observed in the brains of their fetuses. Ketamine-induced neuronal cell death was also observed with early postnatal intraperitoneal or subcutaneous treatment of rat and mice pups, a period of rapid brain growth. In embryo-fetal developmental toxicity studies in rats and rabbits, nasally-administered ketamine did not induce adverse findings in the offspring other than a reduction in fetal body weight in rabbits.

The reader is referred to the full Pharmacology/Toxicology review by Shiny Matthew, Ph.D. and Ikram Elayan, Ph.D.

### Review of Pharmacovigilance Database

The applicant reports that during the clinical trials, eight pregnancies were reported by subjects exposed to esketamine or placebo. All of the subjects were exposed to esketamine in the first trimester, except the case of the blighted ovum which remained blinded at the time of this report. The following outcomes were reported:

- Two pregnancies were ongoing at the time of the applicant's submission; no data were available
- Two ectopic pregnancies (both cases had had some sterilization procedures that were not further described)
- Two spontaneous abortions (gestational age not reported; factors cited complicating these cases were advanced maternal age, previous history of spontaneous abortions, and obesity)

---

<sup>4</sup> Trevino K, et al. Defining treatment-resistant depression a comprehensive review of the literature. *Ann Clin Psychiatry*. 2014;26:222-232.

<sup>5</sup> Rush AJ, et al. Acute and long-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report. *Am J Psychiatry*. 2016;163:1905-1917.

<sup>6</sup> Thase M, Connolly KR. Unipolar depression in adults: management of highly resistant (refractory) depression. Up-to-Date. 11/6/2018. [https://www.uptodate.com/contents/unipolar-depression-in-adults-management-of-highly-resistant-refractory-depression?topicRef=14685&source=see\\_link#H14367195](https://www.uptodate.com/contents/unipolar-depression-in-adults-management-of-highly-resistant-refractory-depression?topicRef=14685&source=see_link#H14367195) accessed 12/26/2018.

- One elective abortion (first trimester; gestational age and reason for termination not described)
- One blighted ovum

There were three pregnancies reported with paternal exposure to esketamine.

- One pregnancy reported a normal delivery of a healthy infant.
- One pregnancy outcome was unknown.
- One pregnancy was ongoing at the time of the applicant's report.

## Review of Literature

### *Applicant's Review of Literature*

The applicant performed a search of the published literature through December 5, 2018, using Embase, Medline, Derwent Drug File and Biosis databases and the following terms, "esketamine," "ketamine," "pregnancy," "pregnancy exposures," and "adverse effects in fetuses, neonates, infants and developing children."

The results of the applicant's search are in Appendix A. Most of these references relate to the use of the anesthetic ketamine during labor and delivery and do not provide long-term follow-up or infant outcomes aside from Apgar scores. The applicant did include a reference of the effects of ketamine anesthesia in infants who were scheduled for one to three outpatient laser surgery treatments for benign facial growths. The infants were assessed using a neurodevelopmental scale (Bayley Scales of Infant Development-Second Edition) prior to the first and after the last surgery. Results showed that scores were lower after the last procedure in infants who experienced three ketamine anesthesia exposures.<sup>7</sup>

### *DPMH Review of Literature*

DPMH conducted a search of the literature using PubMed, Embase, Reprotox, and Micromedex<sup>8</sup> using the search terms, "esketamine" or "ketamine" and "pregnancy," "pregnancy outcomes," "congenital anomalies," "stillbirth," and "spontaneous abortion."

Reprotox<sup>9</sup> references ketamine, but not esketamine and states, "Ketamine administration to pregnant rats or mice induced histologic alterations in fetuses. Use during human pregnancy might have functional effects on the fetus."

Briggs<sup>10</sup> rates ketamine (esketamine is not referenced) as, "Limited Human Data- Animal Data Suggest Low Risk."

A search of the published literature yielded one case of exposure to esketamine during pregnancy that occurred during a clinical trial; that pregnancy was an ectopic pregnancy that was terminated.<sup>11</sup>

<sup>7</sup> Yan J, et al. Repeated exposure to anesthetic ketamine can negatively impact neurodevelopment in infants: a prospective preliminary clinical study. *J Clin Neurol*. 2014;29(10):1333-8.

<sup>8</sup> Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 10/28/2018

<sup>9</sup> 2018 Reproductive Toxicology Center

<sup>10</sup> Briggs GG, Freeman RK. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 10<sup>th</sup> Ed. 2015. Online, accessed 10/28/2018

<sup>11</sup> Daly EJ, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2018;75(2):139-148.

A search of the published literature of pregnancy and ketamine revealed the following papers. Most papers involved exposure at the time of delivery. Individual studies included in the meta-analysis by Heesen, et al.<sup>12</sup> are not included in the table below.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; drug/dose	Outcomes	Comments
Heesen M, et al. <sup>13</sup> 2015 Germany, Switzerland, Finland, Canada	Meta-analysis of 12 randomized controlled double-blind studies of 953 patients (7 studies of spinal anesthesia; 5 on general anesthesia)	Those patients with infant outcomes (not all studies included Apgar scores) - 225 pregnant women treated with either ketamine regional or general anesthesia  125 pregnant controls	At time of delivery	No difference in Apgar scores in exposed vs unexposed infants	No long-term follow-up of infants
Talahma M, et al. <sup>14</sup> 2018 USA	Case report	37-year-old pregnant woman with history of seizures secondary to astrocytoma in status epilepticus	6 weeks 6 days gestation  50-150 mcg/kg/min for 7 days	Normal infant born at 37 weeks, 5 days gestation, delivered by cesarean-section. Apgar scores of 9 and 9 at 1 and 5 minutes, respectively  At 38 weeks post-delivery infant developing normally	Exposed also to propofol, valproate, oxycarbazepine, magnesium sulfate, zonisamide, levetiracetam
Hayaran N, et al. 2018 India	Case report	28-year-old pregnant gestation with acute fatty liver of pregnancy requiring emergency	37 weeks' gestation  Ketamine 25mg IV.	Apgar scores 4, 6 and 7 (at 1, 5, 10 min, respectively)	Decreased fetal movements and patient loss of consciousness required emergency

<sup>12</sup> Heesen M, et al. Intravenous ketamine during spinal and general anesthesia for caesarean section: systemic review and meta-analysis. *Acta Anaesthesiol Scand* 2015;59(4):414-26.

<sup>13</sup> Heesen M, et al. Intravenous ketamine during spinal and general anesthesia for caesarean section: systemic review and meta-analysis. *Acta Anaesthesiol Scand* 2015;59(4):414-26.

<sup>14</sup> Talahma M, et al. Ketamine infusion used to successfully control refractory status epilepticus in a pregnant patient. *Case Rep Neurolog Med.* 2018;Oct 25.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; drug/dose	Outcomes	Comments
		cesarean-section delivery			delivery, no further infant outcomes reported.
Suppa E, et al. 2012 Italy	Double-blind, randomized study	Pregnant women undergoing cesarean-section delivery (s-ketamine n=28, controls N=28)	s-ketamine IV bolus 10 minutes after delivery and for 2 mcg/kg/min continuous IV infusion x 12 hours	No difference between groups regarding patient's ability to breastfeed or duration of breastfeeding. No infant outcomes described.	
Jocelyn AS, et al. <sup>15</sup> 2010 India	Open-label	30 pregnant patients presenting for vaginal delivery	Ketamine bolus 0.1mg/kg bolus at onset of labor followed by infusion of 0.2 mg/kg/hr.	Apgar scores all either 9 or 10 at 5 minutes	No control group, main side effects were increased heart rate and blood pressure
Stoll WD, et al. <sup>16</sup> USA 2012	Case report	21-year-old pregnant patient with multiple pterygium syndrome	Time of delivery, ketamine 50 mg IV, was administered as an adjunct to general anesthesia. (Dose not reported)	Healthy infant delivered with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively	No additional infant follow-up
Pandey R, et al. India 2009	Case report	24-year-old pregnant woman with Eisenmenger's syndrome	35-week's gestation ketamine administered adjunctively with general anesthesia for cesarean-section delivery	Delivered healthy infant with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively	No additional infant follow-up
Lum Hee WC, and Metias VF. <sup>17</sup> UK 2001	Case report	23-year-old pregnant woman with fetal distress, and a history of spina bifida cystica	29 weeks' gestation; Ketamine 400 mg IM administered as part of her anesthesia for emergency	Delivered infant with respiratory distress, requiring intubation. Apgar scores of 5 and 9 at 1 and 5 minutes, respectively	

<sup>15</sup> Joselyn AS, et al. Ketamine for labour analgesia. *Int J Obstet Anesth.* 2010;19(1):122-3

<sup>16</sup> Stoll WD, et al. Anesthetic management of pregnant patient with multiple pterygium syndrome (Escobar type). *Int J Obstet Anesth.* 2012;21(2):197-99.

<sup>17</sup> Hee WC, Metias VF. Intramuscular ketamine in a parturient in who pre-operative intravenous access was not possible. *Br J Anaesth.* 2001;86(6):891-3.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; drug/dose	Outcomes	Comments
			cesarean-section delivery		

FDA Drug Safety Communication regarding General Anesthetics and Sedation Drugs in Pregnant Women<sup>9</sup>

The key messages of the DSC issued by the Agency in December 2016 include the following:

- Repeated or lengthy (greater than 3 hours) use of general anesthetic and sedation drugs in pregnant women and young children during surgery or other procedures may affect the child’s developing brain.
- Parents, pregnant women, care providers, obstetricians, surgeons, and anesthesiologists should be aware of the potential risks that anesthetics and sedation drugs pose to the developing brain and carefully decide on the appropriate timing for potentially elective surgery, particularly for pregnant women in their third trimester and children under three years of age.

*Reviewer comments:*

*Human data on ketamine and esketamine use in pregnancy are largely limited to studies of ketamine administration as an anesthetic at the time of delivery, and a few cases of use during pregnancy in the applicant’s database. There is no long-term follow-up of the exposed infants. Animal data in several species, including primates, indicate that exposure to ketamine in utero is associated with neuronal apoptosis and cognitive deficits in offspring. Based on the animal data and the FDA Drug Safety Communication regarding General Anesthetics and Sedation Drugs in Pregnant Women, esketamine should not be used during pregnancy.*

**LACTATION**

Nonclinical Experience

Racemic ketamine is excreted in cow’s milk. Following a single IV dose of 5mg/kg ketamine in mature Holstein cows, ketamine was detected up to 8 hours in plasma and up to 48 hours in milk. The milk AUC was approximately double the plasma AUC.<sup>18</sup>

The reader is referred to the full Pharmacology/Toxicology review by Shiny Matthew, Ph.D. and Ikram Elayan, Ph.D.

Review of Pharmacovigilance Database

The applicant did not describe any cases related to lactation from their clinical trials.

<sup>18</sup> Sellers G, et al. Pharmacokinetics of ketamine in plasma and milk of mature Holstein cows. J Vet Pharmacol Therap. 2010;33:480-484.

## Review of Literature

### *Applicant's Review of Literature*

The applicant performed a search of the published literature through December 5, 2018, using Embase, Medline, Derwent Drug File and Biosis databases and the following terms, “esketamine,” “ketamine,” “lactation,” and “adverse effects in fetuses, neonates, infants and developing children.”

No cases related to lactation were located in the search.

DPMH conducted a search of *Medications in Mother's Milk*, the Drugs and Lactation Database (LactMed),<sup>19</sup> Micromedex,<sup>20</sup> and of the published literature in PubMed and Embase using the search terms “ketamine” or “esketamine” and “lactation” or “breastfeeding.”

Micromedex<sup>20</sup> states, “Infant risk cannot be ruled out.”

Hale<sup>21</sup> rates ketamine as “L3-No Data-Probably Compatible.” Hale reports there are no data available on the transfer of ketamine into human milk, but that ketamine has a short half-life (2.5 hours) and its redistribution half-life out of plasma (into muscle and other tissues) is brief (10-15 minutes) so milk levels are likely to be low.” Hale does not reference esketamine.

In *Drugs in Pregnancy and Lactation*,<sup>22</sup> Briggs's breastfeeding recommendation is “No human data- probably compatible.” Briggs also states the eliminations half-life of ketamine is 2.17 hours and the drug should be undetectable in milk approximately 11 hours after a dose. Esketamine is not referenced in Briggs.

Ketamine is referenced in the LactMed<sup>19</sup> database, and the Summary of Use during Lactation states, “Breastmilk levels of ketamine have not been measured after administration in humans. Minimal data indicated that ketamine use in nursing mothers may not affect the breastfed infant or lactation. Until more data are available, ketamine should only be used with careful monitoring during breastfeeding. Alternate agents are preferred.” Additional information from LactMed is below:

“Effects in Breastfed Infants:

Four mothers who received epidural analgesia with lidocaine and bupivacaine for cesarean section also received general anesthesia with ketamine and midazolam (dosages

---

<sup>19</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

<sup>20</sup> Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 10/2/2018

<sup>21</sup> Hale, Thomas. *Hale's Medications and Mother's Milk* 2019. Springer Publishing Company, New York, NY.

<sup>22</sup> Briggs GG, Freeman RK. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 10<sup>th</sup> Ed. 2015. Online, accessed 10/2/2018

not specified). Their infants were either breastfed or received their mother's breastmilk by bottle. No adverse effects were reported in the infants.<sup>23</sup>”

“Effects on Lactation and Breastmilk:

A pregnant woman sustained 28% body surface area burns near term. She underwent an emergency cesarean section on her due date under ketamine anesthesia. Although the infant required vigorous resuscitation, the infant began breastfeeding immediately. The infant had transient jaundice that resolved in a few days.<sup>24</sup>

A study compared women undergoing cesarean section who received either placebo or S-ketamine 0.5 mg/kg intramuscularly, followed by a continuous infusion of 2 mcg/kg/minute for 12 hours. This low dose was used to enhance analgesia and reduce residual pain rather than to provide anesthesia. All women received intraspinal bupivacaine 8 to 10 mg and sufentanil 5 mcg for analgesia, as well as midazolam 0.02 mg/kg intravenously before the S-ketamine or placebo injection. Postoperatively, patients received patient-controlled intravenous morphine for 24 hours, followed by acetaminophen, oral ketorolac and a single dose of ondansetron 8 mg intravenously as needed. Of the 56 patients enrolled in the study (28 in each group), 13 in each group were contacted at 3 years postpartum. Patients who received placebo reported breastfeeding for an average of 10.5 months and those who received S-ketamine reported breastfeeding for an average of 8 months; however, the difference was not statistically significant.<sup>25</sup>

A randomized, double-blind study compared the effects of intravenous propofol 0.25 mg/kg, ketamine 0.25 mg/kg, ketamine 25 mg plus propofol 25 mg, and saline placebo for pain control in mothers post-cesarean section in mothers post-cesarean section. A single dose was given immediately after clamping of the umbilical cord. The time to the first breastfeeding was 58 minutes in those who received placebo, 31.9 minutes with ketamine and 25.8 minutes with propofol plus ketamine. The time was significantly shorter than the other groups with the combination.”<sup>26</sup>

A search of the published literature located an on-line document published by Pfizer entitled, “Annex to PSUR Core Safety Profile: S-Ketamine” that states, “S-ketamine is excreted into breast milk, but effects on the child seems unlikely when using therapeutic doses.”<sup>27</sup>

*Reviewer comments:*

*The published literature is almost exclusively on anesthetic doses of ketamine. The dose, route of administration, and chronicity of exposure of the anesthetic ketamine differ from SPRAVATO.*

---

<sup>23</sup> Ortega D, et al. Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. Acta Anaesthesiol Scand. 1999;43:394-7.

<sup>24</sup> Mokube JA, et al. Burns in pregnancy: a case report from Bueas Regional Hospital Cameroon. Pan Afr Med J. 2009;3:2.

<sup>25</sup> Suppe E, et al. A study of low-dose S-ketamine infusion as “preventive” pain treatment for cesarean section with spinal anesthesia: benefits and side effects. Minerva Anesthesiol. 2012;78:774-81.

<sup>26</sup> Jaafarpour M, et al. Effect of ketofol on pain and complication after Caesarean delivery under spinal anesthesia: a randomized double-blind clinical trial. J Clin Diagn Res. 2017;11:UC04-UC-07.

<sup>27</sup> Core Safety Profile S-ketamine (ketamine hydrochloride), Pfizer. May 2009. <https://db.cbgs-meb.nl/veegactie/csp/esketamine-5-2009.pdf> Accessed 11/30/2018.

*SPRAVATO is used at lower doses, but on a chronic basis. Given the animal data suggesting adverse neuronal effects of ketamine at ages equivalent to infancy possibly up to age 3, the concentration in animal milk (M: P ratio ~2), and its known presence in breast milk, DPMH recommends against breastfeeding during treatment with SPRAVATO.*

## ***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

### ***Nonclinical Experience***

Esketamine was administered intranasally to both male and female rats before mating, throughout the mating period, and up to day 7 of gestation at doses equivalent to 4.5, 15, and 45 mg/kg/day (based on a 200g rat), which are approximately, 0.05, 0.3, and 0.6-times the maximum recommended human dose (MRHD) of 84 mg/day based on mean AUC exposures, respectively. Disruptions in estrous cyclicity at the high dose of 45 mg/kg/day, mating delays at 15 mg/kg/day, and preimplantation loss at 4.5 mg/kg/day were observed. The No Observed Adverse Effect Level (NOAEL) for mating and fertility is 4.5 mg/kg/day which is 0.04-times (males) and 0.07-times (females) the exposures at MRHD of 84 mg/day. There was no NOAEL for the observed preimplantation loss.

The reader is referred to the full Pharmacology/Toxicology review by Shiny Matthew, Ph.D. and Ikram Elayan, Ph.D.

### ***Review of Pharmacovigilance Database***

The applicant did not describe any cases related to infertility from their clinical trials.

### ***Review of Literature***

#### ***Applicant's Review of Literature***

The applicant performed a search of the published literature through December 5, 2018, using Embase, Medline, Derwent Drug File and Biosis databases and the following terms, "esketamine," "ketamine," "reproductions," and "fertility."

No references were found related to female fertility or hormonal contraception. Two *in vitro* studies indicate an adverse effect of ketamine on sperm motility.<sup>28 29</sup>

#### ***DPMH Review of Literature***

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, "esketamine" or "ketamine" and "fertility," "contraception," "oral contraceptives," and "infertility."

A search of the published literature yielded four papers on ketamine and infertility. All were papers on the use of ketamine as an anesthetic agent for gynecological laparoscopy for infertility evaluation. No additional data on the effects of ketamine on infertility or hormonal contraception were located in the search.

---

<sup>28</sup> Absalan F, et al. The effects of different doses of ketamine on quality of normal ejaculated sperm. *Int J Fertil Steril.* 2014;8(2):207-214.

<sup>29</sup> He Y, et al. Ketamine inhibits human sperm function by Ca(2+)-related mechanism. *Biochem Biophys Res Commun.* 2016;478(1):501-506.

*Reviewer comments:*

*Animal data indicate an adverse effect of ketamine on fertility. Human data are limited to ketamine's use as an anesthetic for infertility evaluation procedures or in vitro studies with sperm.*

## **DISCUSSION AND CONCLUSIONS**

### Pregnancy

Data related to the chronic use of esketamine in humans are limited to a few cases from the applicant's database. Data on ketamine use in pregnancy are limited to acute use around the time of delivery. Long-term studies of infant outcomes are not available. Animal data indicate that exposure to ketamine *in utero* is associated with neuronal apoptosis and cognitive deficits in exposed offspring in several animal species, including primates. In a discussion between the DPP Nonclinical Team and DPMH held on December 20, 2018, the Nonclinical Team noted that the concern for neuronal apoptosis is not limited to the third trimester of pregnancy and early childhood. Although there are no animal data regarding neuronal apoptosis for the first and second trimesters of pregnancy, there is a theoretical risk of fetal harm based on the drug's mechanism of action and animal data from the later stages of pregnancy and juvenile animal studies.

There are alternative treatments for treatment resistant depression in females of reproductive potential and in pregnant women (See **PREGNANCY: Treatment-resistant Major Depressive Disorder (MDD) in Pregnancy for further details**). Based on the animal data and a recent FDA Safety Communication, DPMH recommends that SPRAVATO not be used during pregnancy and that females of reproductive potential consider pregnancy planning and prevention. Labeling will include the Pregnancy Exposure Registry, Risk Summary, Clinical Considerations, and Data subheadings.

### Lactation

Esketamine is present in human milk; ketamine is present in animal milk. Data from a lactation study in cows indicate that ketamine concentrated in milk at a milk: plasma ratio of >1. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Serum levels of ketamine or esketamine in breastfed infants have not been reported. Studies in juvenile animals indicate an adverse effect of ketamine on neuronal development. DPMH recommends that against breastfeeding during treatment with esketamine.

### Females and Males of Reproductive Potential

Animal data indicate an adverse effect on fertility. However, following email discussions with the nonclinical team,<sup>30</sup> the relevance to humans is not strong enough to be included in 8.3, therefore these data will be kept in subsection 13.1. There are no data in humans indicating an adverse effect of esketamine or ketamine on hormonal contraception or female fertility. Studies of male fertility are limited to two *in vitro* studies on sperm and do not include studies in men exposed to either esketamine or ketamine. Animal data on the adverse effects of ketamine on neuronal development starting in the second trimester of pregnancy. The applicant has included a subsection 8.3 for contraception to minimize the risk of fetal exposure. DPMH agrees with including subsection 8.3 with a subheading for contraception.

---

<sup>30</sup> Personal communication with Shiny Mathew, Ph.D., and Ikram Elayan, Ph.D. 1/25/2019.

## LABELING RECOMMENDATIONS

DPMH revised Highlights and subsections 5.X, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

### DPMH Proposed Pregnancy and Lactation Labeling

## HIGHLIGHTS OF PRESCRIBING INFORMATION

### -----WARNINGS AND PRECAUTIONS-----

- Embryofetal Toxicity: May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential (5.x, 8.1, 8.3)

### -----USE IN SPECIFIC POPULATIONS-----

- Lactation: Breastfeeding not recommended. (8.2)

## FULL PRESCRIBING INFORMATION

### 5 WARNINGS AND PRECAUTIONS

#### 5.X Embryo-fetal Toxicity

Based on findings from animal studies, with a related product, ketamine, SPRAVATO may cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1),(8.2)*]. Advise a pregnant woman of the potential risk to an infant exposed to SPRAVATO in utero. Advise females of reproductive potential to consider pregnancy planning and prevention [see *Use in Specific Populations (8.1),(8.3)*].

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>

##### Risk Summary

There are (b) (4) data on SPRAVATO use in pregnant women to (b) (4) drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on findings (b) (4) animal studies with (b) (4), ketamine, SPRAVATO may cause fetal harm (see *Data*). (b) (4)

(b) (4) advise pregnant women of the potential risk to (b) (4). There are risks to the mother associated with untreated depression in pregnancy (see *Clinical Considerations*).

In embryofetal reproduction studies in rabbits, skeletal malformations were noted at (b) (4) doses of intranasally administered ketamine with estimated esketamine exposures (b) (4) at the maximum recommended human dose (MRHD) of 84 mg/day. In addition, intranasal

administration of esketamine to pregnant rats during pregnancy and lactation at exposures that were similar to the MRHD resulted in a delay in sensorimotor development in pups during the preweaning period and a decrease in motor activity in the postweaning period.

(b) (4)

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15-20%, respectively.

### Clinical Considerations

#### *Disease-associated maternal and/or embryo/fetal risk*

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

### Data

#### *Animal Data*

(b) (4)

When female monkeys were treated intravenously with ketamine at high anesthetic dose levels in the third trimester of pregnancy, neuronal cell death was observed in the brains of their fetuses.

(b) (4)

This period of brain development translates into the third trimester of human pregnancy. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits

Racemic ketamine was administered intranasally to pregnant rats and rabbits during the period of organogenesis at doses (b) (4). The No Observed Adverse Effect level (NOAEL) for embryofetal toxicity in rats was the highest dose of 150 mg/kg/day.

(b) (4)

(b) (4) the NOAEL associated with esketamine plasma exposure (AUC) is 12-times the AUC exposure at the MRHD of 84 mg/day. In rabbits, the high dose was lowered from 100 to 50 mg/kg (b) (4) due to excessive mortality in (b) (4). Skeletal malformations were observed at (b) (4) doses (b) (4).

(b) (4)

(b) (4)

Administration of esketamine HCl to pregnant rats during pregnancy and lactation at intranasal doses equivalent to 4.5 to 45mg/kg/day which are 0.07 times to 0.7 times the MRHD of 84 mg/day based on AUC, (b) (4)

(b) (4) In addition, a dose response delay in the age of attainment of Preyer response reflex observed in pups at all doses during the preweaning period (b) (4)

This sensory/motor developmental measure was tested starting on postnatal day (PND) (b) (4)

During the postweaning period, a decrease in motor activity was observed  $\geq 15$  mg/kg which is 0.5-times the human exposure at the MRHD of 84 mg/day. The NOAEL (b) (4) was associated with plasma exposure (AUC) 0.07-times the AUC exposures at the MRHD of 84 mg/day.

## 8.2 Lactation

### Risk Summary

Esketamine is present in human milk. There are no data on the effects of esketamine on the breastfed infant or the effects on milk production. Published studies in juvenile animals report neurotoxicity (*see Data*). Because of the potential for (b) (4) neurotoxicity, advise patients that breastfeeding is not recommended during treatment with SPRAVATO.

### Data

Published juvenile animal studies demonstrate that the administration (b) (4) drugs, (b) (4) that (b) (4) block NMDA receptors (b) (4) during the period of rapid brain growth or synaptogenesis, results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of (b) (4) life but may extend out to approximately 3 years of age in humans.

## 8.3 Females and Males of Reproductive Potential

### Contraception

Based on animal reproduction studies, SPRAVATO may cause embryofetal harm when administered to a pregnant woman [(see *Warnings and Precautions (5.x)* and *Use in Special Populations (8.1)*]. However, (b) (4) how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential.

## 17 PATIENT COUNSELING INFORMATION

### Pregnancy

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise patients to notify their healthcare provider if they are pregnant or intend to become pregnant during treatment with SPRAVATO. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SPRAVATO during pregnancy [see *Use in Specific Populations (8.1)*].

Lactation

Advise women not to breastfeed during treatment with SPRAVATO [see *Use in Specific Populations (8.2)*]

**APPENDIX A – Results from Applicant’s Literature Search**

Literature citation	Key Findings
<b>Fertility</b>	
Absalan et al 2014	<ul style="list-style-type: none"> <li>• Prospective study of 40 males with normal semen sample</li> <li>• Evaluated effects of ketamine on membrane integrity, DNA fragmentation and sperm parameters in humans</li> <li>• Subjects randomly allocated to four groups (Control and case I, II and III) whose semen samples were adjusted to different concentrations of ketamine (1, 3, 5 µL) for one hour</li> <li>• Total sperm motility in all case groups were significantly lower compared with the control group</li> <li>• In case group III, progressive motility showed significant difference with case group II</li> <li>• After addition of ketamine, sperm had evidence of coiled tails in all case groups compared to control group however this observation was not significant</li> <li>• Evaluation of membrane integrity showed the rate of necrospemia increased in all case groups. However, ketamine only significantly affected membrane integrity in case group III</li> <li>• Conclusion: Ketamine, through its effect on membrane integrity and DNA fragmentation, decreased sperm viability and caused abnormal sperm parameters in progressive motility</li> </ul>
He et al 2016	<ul style="list-style-type: none"> <li>• Authors investigated in vitro effects of ketamine on human sperm functions, to elucidate the underlying mechanism.</li> <li>• Human sperm were treated in vitro with different concentrations of ketamine (0, 0.125, 0.25, 0.5, 1 g/L). The results showed that 0.25-1 g/L ketamine inhibited sperm total motility, progressive motility and linear velocity, in a dose-dependent manner. In addition, the sperm's ability to penetrate viscous medium was significantly inhibited by ketamine. Ketamine did not affect sperm viability</li> <li>• The intracellular calcium concentration, which is a central factor in the regulation of human sperm function, was decreased by ketamine (0.125-1 g/L) in a dose-dependent manner. Furthermore, the currents of the sperm-specific calcium channel, CatSper, which modulates calcium influx in sperm, were inhibited by ketamine (0.125-1 g/L) in a dose-dependent manner.</li> <li>• Authors suggested that ketamine induces its toxic effects on human sperm functions by reducing sperm intracellular calcium concentration through inhibition of CatSper channel</li> </ul>
<b>Use during pregnancy</b>	
Bolnick and Rayburn 2003	<ul style="list-style-type: none"> <li>• Authors reviewed various effects related to pregnancies complicated by substance use in general</li> <li>• Ketamine is listed as one of the hallucinogens substance use disorder in women during pregnancy in the context of impact in utero exposure of specific substances on the fetus and newborn infant</li> </ul>

Literature citation	Key Findings
Friedman 1988	<ul style="list-style-type: none"> <li>• Authors presented a review of exposure of women to anesthetic agents early in pregnancy</li> <li>• Authors stated no epidemiological studies of congenital anomalies in children born to women exposed to ketamine during pregnancy have been reported</li> <li>• Authors referred to preclinical data showing the frequency of malformation was not increased among the offspring of rats treated during pregnancy with ketamine in doses more than ten times greater than those used in humans</li> <li>• This review article does not suggest teratogenic effect of ketamine</li> </ul>
Galloon 1973	<ul style="list-style-type: none"> <li>• Authors measured uterine pressure, intensity and frequency of contractions in a pregnant uterus before and after intravenous injection of ketamine HCl in 12 patients who were between 8 and 19 weeks pregnant</li> <li>• In every one of 12 patients, the uterine pressure was higher after ketamine suggesting contracted uterus along increased frequency and intensity of the contractions</li> <li>• Effects lasted between 5 and 15 minutes after single ketamine injection</li> </ul>
Galloon 1976	<ul style="list-style-type: none"> <li>• Five patients were administered different successive doses of ketamine</li> <li>• Lower doses increased the individual uterine contractions while higher doses increased the basal tone as well</li> <li>• The author notes that when the total dose of ketamine has been larger than 1 mg/kg, the Apgar scores have been unacceptable secondary to dose related increase in uterine tone</li> </ul>
Gimovsky et al 2018	<ul style="list-style-type: none"> <li>• The authors describe 2 pregnant patients with sickle cell crisis receiving ketamine for pain control</li> <li>• In both cases, Apgar scores were normal, and no other adverse events were reported</li> <li>• The authors discuss the major side effects that limit ketamine use are psychomimetic, such as hallucinations; cardiovascular, mainly hypertension and tachycardia; and dizziness</li> <li>• These cardiovascular side effects are unlikely at low doses used for pain control; however, hallucinations and dizziness may limit ketamine's use as an analgesic</li> </ul>
Gin 1993	<ul style="list-style-type: none"> <li>• The authors review effects of general anesthetics, including ketamine, during pregnancy or for delivery</li> <li>• The author discusses placental transfer, fetal and neonatal elimination, and transfer to breast milk of anesthetics</li> <li>• Since anesthetics are given for a short duration, the author argues referring to existing literature that even if transfer to milk occurs, the amount of drug is very low and no adverse neonatal effects are expected</li> </ul>

Literature citation	Key Findings
	<ul style="list-style-type: none"> <li>• The listed effects for the hallucinogens include lack of anomalies, intrauterine withdrawal with increased fetal activity, depressed breathing movements, preterm delivery, preterm rupture of the membranes, fetal growth restriction, meconium-stained amniotic fluid, perinatal mortality</li> <li>• Ketamine's effect on increased heart rate is mentioned in the context of drug overdose and withdrawal in pregnant women</li> <li>• There are no findings suggestive of a ketamine-specific effect or signal</li> </ul>
Cappell 2006	<ul style="list-style-type: none"> <li>• Authors reviewed ketamine's properties as an anesthetic</li> <li>• Ketamine rapidly crosses placenta to fetus in humans</li> <li>• Ketamine administration during delivery occasionally causes maternal dysphoria</li> <li>• Ketamine has oxytocic effects, causes an increased basal uterine tone as well as increased frequency and amplitude of uterine contractions, and can increase the blood pressure in the mother</li> <li>• Both the uterine and blood pressure effects are transient, short lasting, and dose-dependent</li> <li>• Maternal ketamine administration just before delivery does not adversely affect neonatal blood pressure</li> <li>• Ketamine administration during delivery can cause transient neonatal depression, reflected in lower initial Apgar scores</li> <li>• The phenomenon is most evident with high dose administration and prolonged induction-to-delivery times. The neurobehavioral depression may last for up to 2 days after delivery</li> <li>• Maternal ketamine administration during labor, however, appears to cause less neonatal respiratory depression than other sedatives</li> <li>• High doses of ketamine administered to the mother during delivery can transiently increase neonatal muscle tone</li> <li>• Ketamine has not been associated with teratogenicity, but administration during the first trimester has not been reported</li> <li>• Ketamine is rated as a class B drug during pregnancy, but carries the caveats that fetal safety during organogenesis is unstudied in humans, and extremely high or prolonged administration during pregnancy might be unsafe</li> </ul>
Cosmi et al 1983	<ul style="list-style-type: none"> <li>• Authors reviewed effect of anesthetics on uteroplacental blood flow and fetus</li> <li>• Ketamine does not alter uterine blood flow or fetal breathing movements and acid-base status when administered to mothers in doses less than 2 mg/kg</li> <li>• When given in higher doses, ketamine may cause maternal hyperventilation and uterine hyperactivity and hence cause a reduction in uteroplacental blood flow and fetal asphyxia</li> </ul>

Literature citation	Key Findings
	<ul style="list-style-type: none"> <li>• The review specific to ketamine (used alone or in combination with nitrous oxide and inhalational agents, as an alternative to thiopental) suggests that the clearance of ketamine was reported to be lower in pregnant women (48 ml/kg/min) than in nonpregnant controls (68 ml/kg/min) but these values are abnormally high and are calculated from only the first 30 min of concentration data</li> <li>• There was a lower incidence of maternal awareness after ketamine compared with thiopental and the incidence of dysphoric reactions or hallucinations was low</li> <li>• Neonatal neurobehavioural scores were also satisfactory</li> <li>• Ketamine may increase uterine tone and concerns about dysphoric reactions remain</li> </ul>
Horta and Lemonica 2002	<ul style="list-style-type: none"> <li>• Authors reviewed information on placental transfer and embryo-fetal effects of drugs used in anesthesia</li> <li>• Ketamine in cesarean section anesthesia may result in hypertension and tachycardia, making it inadequate for pre-eclampsia or eclampsia patients</li> <li>• Ketamine may be a good agent for anesthesia induction, especially in hypovolemic patients and does not affect the fetus if doses does not exceed 1.5 mg/kg</li> </ul>
Kuczkowski 2006	<ul style="list-style-type: none"> <li>• A comprehensive review on safety of anesthetics in pregnant women, including ketamine</li> <li>• Authors suggested that ketamine is a very useful induction agent in obstetric patients due to its rapid onset of action, provides both analgesia and hypnosis, and it reliably provides amnesia</li> <li>• Clinical studies have suggested that the use of ketamine is associated with a decreased incidence of maternal awareness when compared with administration of thiopental</li> <li>• Authors suggested that ketamine should be avoided in hypertensive patients</li> <li>• The author observed that large doses of ketamine increase uterine tone. However, an induction dose of 1 mg/kg does not increase uterine tone</li> <li>• Ketamine rapidly crosses the placenta, and it reaches a maximum concentration in the fetus ~ 1.5 – 2.0 minutes after administration</li> </ul>
Mattingly et al 2003	<ul style="list-style-type: none"> <li>• In this review article, the authors noted that ketamine crosses the placenta but in maternal doses less than 1.5 mg/kg it does not cause neonatal respiratory depression</li> </ul>
Oats et al 1979	<ul style="list-style-type: none"> <li>• Prospective study on 19 women investigating ketamine's effect on pregnant uterus</li> <li>• Those women who received 2 mg/kg of ketamine had increase in intra-uterine pressure</li> </ul>

Literature citation	Key Findings
Rayburn 2007	<ul style="list-style-type: none"> <li>• The author presented outcome data in hallucinogen users including ketamine</li> <li>• No anomalies were reported however possible increase spontaneous abortion was noted</li> </ul>
Singer et al 2012	<ul style="list-style-type: none"> <li>• Authors reported results of a prospective study in poly drug users including “ecstasy” and ketamine</li> <li>• Prenatal heavy MDMA or ecstasy exposure among poly drug abusers including ketamine showed persistent neurotoxic effects on motor development</li> <li>• No specific data with ketamine included in the publication.</li> </ul>
Stevenson 2005	<ul style="list-style-type: none"> <li>• In this review of ketamine, the author noted that no specific reproductive studies have been performed in human to investigate teratogenic effect of ketamine in early pregnancy</li> </ul>
Weinberg et al 2005	<ul style="list-style-type: none"> <li>• The authors presented data on ketamine properties</li> <li>• It rapidly crosses the placenta but tends not to produce neonatal depression in maternal doses less than 1 to 1.5 mg/kg</li> </ul>
<b>Use during delivery/neonatal period</b>	
Baraka et al 1990	<ul style="list-style-type: none"> <li>• Prospective study where ketamine was used as sole anaesthetic in 20 full-term patients undergoing elective Caesarean section</li> <li>• Intravenous administration of ketamine 1.5 mg.kg-1 was followed by succinylcholine 1.5 mg.kg-1 and tracheal intubation</li> <li>• Apgar scores of newborns at one and five minutes, as well as their umbilical vein blood gases were also evaluated and correlated with the induction-to-delivery (I-D) and the uterine incision-to-delivery (U-D) intervals</li> <li>• The newborns of group A (I-D&lt;10 min, U-D&lt;90 sec) showed higher Apgar scores at one minute, as well as higher umbilical vein PO2 than was achieved in Group B (I-D≥10 min, U-D≥90 sec)</li> <li>• It was concluded that the technique used was not associated with maternal awareness or neonatal depression, provided that the I-D interval was less than 10 min and the U-D interval was less than 90 seconds</li> <li>• The finding suggested lack of ketamine-induced neonatal depression</li> </ul>
Bhutta et al 2012	<ul style="list-style-type: none"> <li>• Prospective study in which 24 infants, without chromosomal abnormalities received ketamine (2 mg/kg, n = 13) or placebo (saline, n = 11) before cardiopulmonary bypass for repair of ventricular septal defects</li> <li>• Compared plasma markers of inflammation and CNS injury at end of surgery, and 6, 24 and 48 hr after surgery</li> <li>• MRI and spectroscopy were performed before cardiopulmonary bypass and at the time of hospital discharge in a subset of infants (n=5 in each group)</li> </ul>

Literature citation	Key Findings
	<ul style="list-style-type: none"> <li>• Cerebral hemodynamics were monitored postoperatively using near-infrared spectroscopy, and neurodevelopmental outcomes were assessed using Bayley Scales of Infant Development-II before and 2–3 weeks after surgery</li> <li>• Statistically significant differences were noted in preoperative inspired oxygen levels, intraoperative cooling and postoperative temperature, respiratory rate, platelet count, and bicarbonate levels</li> <li>• No significant differences were noted in the expression of various inflammatory markers or markers of CNS injury</li> <li>• MRI with spectroscopy showed that ketamine administration led to a significant decrease in choline and glutamate plus glutamine/creatine in frontal white matter</li> <li>• No statistically significant differences occurred between pre- and postoperative Bayley Scales of Infant Development-II scores</li> <li>• No evidence for neuroprotection or neurotoxicity</li> </ul>
Briggs 2002	<ul style="list-style-type: none"> <li>• Author reviewed effects of different drugs considered to cause toxicity in the fetus and/or breast-fed newborns</li> <li>• Ketamine listed among drugs that cause dose-related CNS depression</li> <li>• No other evidence or supporting data are included in the article</li> </ul>
Dunn et al 1973	<ul style="list-style-type: none"> <li>• The authors report uses of ketamine in termination of pregnancy where ketamine use was free of respiratory and circulatory complications</li> <li>• Seventy-five patients were anaesthetized for termination of pregnancy by suction curettage using 4 methods of anesthesia</li> <li>• Blood loss was measured with a hemoglobin dilution technique</li> <li>• Authors suggested that the use of ketamine is associated with a low blood loss, is easy to administer, and appears to be reasonably free of respiratory and circulatory complications, provided that the patient is not hypertensive</li> <li>• Despite injecting diazepam 5 mg intravenously at the end of the operation, 6 of 18 patients reported that they suffered unpleasant psychic sensations either while under the anesthetic, or on awakening</li> </ul>
Heesen et al 2015	<ul style="list-style-type: none"> <li>• Systematic review and meta-analysis covering 12 randomized double-blind trials with 953 patients undergoing caesarian section who received ketamine</li> <li>• Neonatal outcome as assessed by Apgar scores or umbilical cord pH did not differ between babies of ketamine-treated and control group mothers; however, there were only limited data available</li> <li>• Authors found a higher incidence of diplopia and nystagmus after ketamine use in the regional anesthesia groups</li> </ul>

Literature citation	Key Findings
Joel et al 2014	<ul style="list-style-type: none"> <li>• Double-blind placebo-controlled study in 70 patients in labor receiving low dose ketamine</li> <li>• A loading dose of ketamine (0.2 mg/kg) was followed-by an infusion (0.2 mg/kg/h) until the delivery of the neonate. Similar volume of saline was infused in the placebo-group</li> <li>• There was no significant clinical change in the maternal hemodynamics and fetal heart rate.</li> <li>• All the neonates were breast fed and the umbilical cord blood pH was between 7.1 and 7.2</li> <li>• The authors concluded that a low-dose ketamine infusion could provide acceptable analgesia during labor and delivery</li> </ul>
Joselyn et al 2009	<ul style="list-style-type: none"> <li>• Prospective trial to assess the efficacy and safety of a low-dose ketamine infusion for labor analgesia in 30 mixed-parity parturients with no antenatal risk factors and expected to have normal vaginal deliveries</li> <li>• Ketamine infused for labor analgesia showed a decreasing trend for pain score, although approximately half of the ketamine group experienced light headedness</li> <li>• All the neonates were breast fed</li> <li>• There was no significant clinical change in the maternal hemodynamics or fetal heart rate</li> <li>• Apgar scores were 9 or 10 at 5 min in all neonates and the mean cord blood pH was <math>7.207 \pm 0.007</math> (range: 7.05–7.35)</li> </ul>
Kose et al 2013	<ul style="list-style-type: none"> <li>• Prospective, randomized, double-blinded, placebo-controlled study in 120 patients scheduled for Cesarean delivery during spinal anesthesia</li> <li>• Patients were randomized to three groups: saline (Group C, n=30), intravenous (IV) ketamine 0.25 mg/kg (Group K-0.25, n=30), or IV ketamine 0.5 mg/kg (Group K-0.5, n=30)</li> <li>• Grade 3 or 4 shivering was treated with IV meperidine 25 mg and the prophylaxis was regarded as ineffective</li> <li>• The number of shivering patients was significantly less in Group K-0.25 and in Group K-0.5 than in Group C (P = 0.001, P = 0.001, respectively). The tympanic temperature values of Group C were lower at all times of the study than in either ketamine group</li> <li>• Median sedation scores of Group K-0.5 were significantly higher than in Group K-0.25 or Group C at 10, 20, 30, and 40 minutes after spinal anesthesia.</li> <li>• Apgar score was 8 at 1 min and 9 at 5 min in both groups</li> <li>• Throughout the study, HR and SpO2 values were similar among the groups</li> </ul>

Literature citation	Key Findings
Little et al 1972	<ul style="list-style-type: none"> <li>• Prospective study to determine safety of ketamine to mother and baby at labor and delivery in 18 nonpregnant and 14 pregnant subjects</li> <li>• 6 of 14 pregnant patients who had also received pre-medication of meperidine and hydroxyzine was associated with Apnea resulting from excessive rate of administration of initial dose of ketamine.</li> <li>• Neonatal depression was observed in newborns exposed to higher dose of ketamine (2.2 mg/kg followed by 0.11mg/kg per minute).</li> <li>• Recovery of mother and infant was uneventful after awakening.</li> <li>• No long-term follow-up of infant is reported in the paper</li> </ul>
Maduska and Hajghassemali 1978	<ul style="list-style-type: none"> <li>• Prospective study investigating arterial blood gases in mothers and infants at labor during ketamine anesthesia</li> <li>• 20 subjects received either 1 mg/kg IV ketamine or control for vaginal delivery</li> <li>• Infants in both groups had Apgar score of 8 or over at 1 min</li> <li>• No difference between control and ketamine group in either mother or infants with regards to pH, Pco2, P02 or APGAR scores was seen</li> </ul>
Mahomedy et al 1976	<ul style="list-style-type: none"> <li>• Prospective study of 50 mothers who received 2 mg/kg ketamine at Caesarean section</li> <li>• Eight of the 50 infants delivered had neonatal depression assessed on a modified APGAR score. Umbilical cord blood gas analysis showed the presence of a fetal respiratory acidosis. 4 of 5 more severe were considered to be due to in-expert laryngeal suction as no evidence of biochemical asphyxia was found.</li> <li>• No long-term follow-up of infant is reported in the paper</li> </ul>
Meer et al 1973	<ul style="list-style-type: none"> <li>• Prospective study in 68 patients receiving ketamine (2mg/kg) during elective or emergency caesarian section</li> <li>• The Apgar scores recorded suggested that ketamine does not depress the baby</li> <li>• No long-term follow-up of infant is reported in the paper</li> </ul>
Peltz and Sinclair 1973	<ul style="list-style-type: none"> <li>• In a case series of 100 patients undergoing caesarian section, similar incidence of fetal distress was observed in ketamine 1mg/kg or thiopentene 3mg/kg</li> <li>• No significant difference was seen in uterine contractility, neonatal depression, unpleasant dreams, postpartum psychosis or adverse events on the uterus</li> <li>• No long-term follow-up of infant is reported in the paper</li> </ul>
Shabana et al 2012	<ul style="list-style-type: none"> <li>• Placebo-controlled randomized double-blind study</li> <li>• Two hundred twenty-nine patients undergoing caesarian section were randomly allocated into two equal groups: the ketamine group; in which 0.5 mg/kg was infused intravenously in 20 min and the placebo group; in which normal saline was infused</li> </ul>

Literature citation	Key Findings
	<ul style="list-style-type: none"> <li>• Apgar scores at 1 and 5 min were not different between the groups, there was no difference in sedation levels</li> <li>• No long-term follow-up of infant is reported in the paper</li> </ul>
Spigset 1994	<ul style="list-style-type: none"> <li>• In this review paper, the author reviewed excretion of anesthetic agents in breast milk</li> <li>• Drug disposition in the newborn and infant is described.</li> <li>• The author argued that risks of ketamine exposure to suckling infants are very low.</li> <li>• No safety data nor exposure information on ketamine is reported</li> </ul>
Suppa et al 2012	<ul style="list-style-type: none"> <li>• Double blind randomized study for preventative pain treatment in women undergoing elective repeat cesarean section with spinal anesthesia</li> <li>• Patients received either S-Ketamine 0.5mg/kg intramuscular bolus followed by 2microgram/kg/min 12 hr infusion + midazolam 0.02mg/kg (n=28) or placebo (n=28). S-ketamine reduced post op morphine use</li> <li>• No difference in hemodynamics between groups was observed</li> </ul>
Verstraete and Van De Velde 2012	<ul style="list-style-type: none"> <li>• Review paper on commonly used medication for post caesarean analgesia</li> <li>• No detrimental effect on uterine blood flow or fetal hemodynamics has been demonstrated at clinically relevant doses of ketamine</li> <li>• Ketamine is easily transferred from placenta, yet intravenous doses up to 2 mg/kg do not lead to reduced Apgar scores in the neonate.</li> <li>• The authors reported that they were not aware of any published data on ketamine's transfer in human breast milk</li> </ul>
<b>Child Development (no pregnancy exposure data)</b>	
Loepke and Soriano 2008	<ul style="list-style-type: none"> <li>• Systematic review of general anesthetics on developing brain structure</li> <li>• There are no data regarding effects of administration of clinical doses of ketamine in young children on brain structure</li> </ul>
Yan et al 2014	<ul style="list-style-type: none"> <li>• Study in infants who were scheduled for 1 to 3 outpatient laser surgery treatments of benign facial growths with ketamine anesthesia</li> <li>• Patients were assigned to the Ket1, Ket2, or Ket3 group, according to the number of treatments. The Bayley Scales of Infant Development–Second Edition (BSID-II) was used to assess neurodevelopmental outcomes before the first and after the last therapy showing scores after the last procedure were lower than those before the first surgery in the Ket3 group (P &lt; .05)</li> <li>• Results suggest that 3 or more exposures to anesthetic ketamine have the potential to adversely affect neurodevelopment in infants</li> </ul>

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/  
-----

CATHERINE A ROCA  
01/25/2019 01:10:30 PM

MIRIAM C DINATALE  
01/25/2019 01:57:36 PM

LYNNE P YAO  
01/30/2019 05:31:56 PM

---

**HUMAN FACTORS REPORT AND LABEL AND LABELING REVIEW**  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

---

<b>Date of This Review:</b>	January 14, 2019
<b>Requesting Office or Division:</b>	Division of Psychiatry Products (DPP)
<b>Application Type and Number:</b>	NDA 211243
<b>Product Type:</b>	Drug-device Combination Product
<b>Drug Constituent Name and Strength</b>	Spravato (esketamine) nasal spray 28 mg
<b>Device Constituent:</b>	Nasal Spray
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Janssen Pharmaceuticals, Inc.
<b>Submission Date:</b>	September 4, 2018, November 20, 2018
<b>OSE RCM #:</b>	2018-1875 and 2018-1873
<b>DMEPA Safety Evaluators:</b>	Nicole Garrison, PharmD, BCPS Loretta Holmes, BSN, PharmD
<b>Acting DMEPA Team Leader:</b>	Teresa McMillan, PharmD
<b>DMEPA Deputy Director:</b>	Irene Chan, PharmD, BCPS

## 1 REASON FOR REVIEW

This review is written in response to a request from the Division of Psychiatry (DPP) to review the human factors (HF) validation study results and labels and labeling submitted as part of the 505(b)(1) submission for Spravato (esketamine) nasal spray (NDA 211243) to address areas of vulnerability that may lead to medication errors.

### 1.1. PRODUCT DESCRIPTION

Spravato (esketamine) nasal spray is a single-use product intended for treatment resistant depression [REDACTED] (b) (4)

[REDACTED] Spravato is intended for administration by patients under the supervision of a healthcare providers (HCP) in a hospital or clinic setting

Janssen proposes the product be supplied in a nasal spray device that contains 2 sprays per device, with each spray containing 14 mg of esketamine. The proposed packaging will be a carton containing one 28 mg nasal spray device (28 mg total dose), a carton containing two 28 mg nasal spray devices (56 mg total dose), and a carton containing three 28 mg nasal spray devices (84 mg total dose). (See Appendices A and E).

### 1.2. REGULATORY HISTORY

We previously reviewed the proposed HF validation study protocol under IND 114345<sup>a</sup> and conveyed our recommendations to Janssen. After further correspondence between Janssen and the FDA, Janssen agreed to implement all of the recommendations in their HF validation study protocol.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A

<sup>a</sup> Holmes, L. Human Factors Protocol Review for Esketamine Nasal Spray IND 114345. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 19. RCM No.: 2016-1230.

<b>Table 1. Materials Considered for this Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Background Information Previous HF Reviews	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

### **3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED**

Our assessment of the HF validation study results, prescribing information (PI), and Instructions for Use (IFU), container labels and carton labeling for Spravato (esketamine) injection is described below.

#### **3.1. HF VALIDATION STUDY RESULTS AND ANALYSES**

Table 2 describes the errors/close calls/use difficulties observed in the HF study, the Applicant's reporting of the results and proposed mitigations, and DMEPA's analyses and recommendations. According to Janssen, based on their use-related risk analysis (URRA), no tasks were determined to be critical, i.e. likely to cause serious injury or serious adverse effects. However, we disagree with Janssen's determination since failure to receive the intended dose would compromise medical care as the patient would not receive the intended benefit from their prescribed therapy. Additionally, we note the Applicant has revised carton labeling to address the use errors observed in the study; however, the Applicant did not provide data to demonstrate the mitigations are effective and do not introduce new risks for use-related error.

Table 2: Analyses of Task Use Errors, Close Calls, and Use Difficulties for Spravato Human Factors Validation Studies					
Critical Tasks	Number of Failures/Use Errors, Close Calls and Use Difficulties		Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant’s Root Cause Analysis and Discussion of Mitigation Strategies	DMEPA’s Analysis and Recommendations
	Trial 1(IFU available, not required)	Trial 2 (IFU required)			
<p><i>Task 1.1</i></p> <p>Patient blows nose before first device only</p>	<p><u>Use Errors</u></p> <p>10</p> <p>(b) (6)</p>	<p><u>Use Errors</u></p> <p>2</p> <p>(b) (6)</p>	<p><b>Trial 1</b></p> <p>Patient did not blow nose before use of the first device</p> <p>(b) (6)</p> <p><b>Trial 2</b></p> <p>(b) (6): patient did not blow nose</p>	<p><b>Trial 1</b></p> <p>(b) (6) HCP said that it was an oversight and mentioned that he had not seen the instruction to have the patient blow their nose until looking at the IFU after use of the device had completed. The HCP knew that during actual use the patient should blow their nose before first using.</p> <p>(b) (6) HCP said the step is missable in the IFU because it is part of preparation, and not part of use.</p> <p>(b) (6) HCP said she was more focused on the patient having his head tilted back and the functionality of the device than the patient blowing his nose. Additionally, she indicated that she had focused on Steps 2 and 3 because they involved the participant and the administration of the drug, while the instruction to blow the nose was in Step 1.</p> <p>(b) (6) HCP indicated she had not seen in the instructions beforehand that the patient should blow their nose until reviewing the IFU afterward. The HCP said the instruction itself did not stand out and</p>	<p>The potential harm associated with not blowing your nose before first device only is an underdose and the patient may not realize the full effect of the treatment.</p> <p>We reviewed Step 1-“Get ready” of the IFU and note that HCPs are advised before first device use: <b>instruct patient to blow nose before first device only</b> and confirm required number of devices. The text is accompanied by an illustration of a tissue box and 3 nasal spray devices. The Applicant proposes no mitigation strategy for the IFU.</p> <p>Based on the root cause analysis information and subjective feedback received, we recommend that the first image and instruction in Step 3 “Prepare Patient” should be instructing the “...patient to blow nose before first device only.” This may help to minimize the risk</p>

Table 2, specific participants are referred to using an alphanumeric code. The letters preceding each number indicate the group to which the participant belongs:

\*P: patient

HCP: healthcare provider

			<p>before use of the first device.</p> <p>(b) (6): HCP suggested patient blow nose after using the 1<sup>st</sup> device.</p>	<p>an image of someone blowing their nose would be better to get her attention while reading the IFU.</p> <p>(b) (6): HCP said it was clear in the IFU but it's too much to remember to teach everything the first time using the device.</p> <p>(b) (6) HCP independently recognized that she should have had patient blow nose first before use after first device had been used. She said that she had just forgotten to mention it to the patient.</p> <p>(b) (6) HCP saw step in the IFU but did not teach it to the patient saying there was a lot to remember to teach for the first time.</p> <p>(b) (6): HCP said he read in the instruction previously but skipped it while engaged with the patient. Location of instruction for patient to blow their nose in "Get ready" section was not sufficient because the HCP would assume "Get ready" was for him. The instruction to have to have the patient blow their nose should be in the "Prepare patient" section instead because it pertains to them.</p> <p>(b) (6): HCP said she read the instruction to have the patient blow their nose while reviewing the IFU originally, but that she forgot. HCP said that unlike each of the steps in the IFU, Step 1 contains two steps and images, which made it less straightforward to remember. She said that the step to have the patient blow their nose should be incorporated within "Step 3: Prepare patient" since that is a necessary step for preparing the patient.</p> <p>(b) (6): HCP assumed the instruction in the IFU meant to blow nose if needed.</p>	<p>for this instruction being overlooked or not carried out.</p> <p><b><u>We provide specific IFU recommendations in Table 4 of the review to address our concern.</u></b> This revision should be incorporated in the user interface and validated in another HF validation study (see section 4.1).</p>
--	--	--	---	--	---

Table 2, specific participants are referred to using an alphanumeric code. The letters preceding each number indicate the group to which the participant belongs:  
 \*P: patient                      HCP: healthcare provider

				<p><b>Trial 2</b></p> <p>(b) (6): HCP and patient read through instructions together and the HCP did not instruct the patient to blow nose. The patient couldn't remember whether she blew her nose. She said she may have forgotten or felt she did not need to blow her nose because it did not feel congested.</p> <p><i>Mitigation strategies:</i></p> <p>No further device design mitigation is possible; only the product labeling can influence the HCPs ability to comprehend this instruction which currently features an instruction and graphic in the IFU.</p> <p>The risk level with this current mitigation is acceptable as supported by clinical study TRD1007 which demonstrated that pretreatment of subjects with history of allergic rhinitis and pre-exposed to grass pollen 1 hour prior to nasal administration of esketamine had no effect on the pharmacokinetics of esketamine.</p>	
<p><i>Task 1.2</i></p> <p>HCP selects 2 devices</p>	<p><u>5 Use Errors</u></p> <p>(b) (6)</p>	0	<p><b>Trial 1</b></p> <p>HCP did not select 2 devices</p> <p>(b) (6)</p>	<p><b>Trial 1</b></p> <p>(b) (6): said he had never seen a device in which 1 complete dose would be provided over 2 separate kits (nasal spray devices), especially if administering a long-lasting medication.</p> <p>(b) (6): assumed each spray was 28 mg, saying the green dots were misleading and he has never had a nasal spray system that has two devices needed. Said the box should say 56 mg, or 28x2.</p>	<p>The potential harm associated with selecting the incorrect number of devices is improper dose (underdose or overdose), resulting in a patient not realizing the full effect of the treatment for depression or, the patient may experience side effects if an overdose occurs, which may include dissociative symptoms, hallucinations, nausea, and vomiting. The submitted root cause information indicates that the</p>

Table 2, specific participants are referred to using an alphanumeric code. The letters preceding each number indicate the group to which the participant belongs:

\*P: patient

HCP: healthcare provider

	<p><u>1 Close Call</u></p> <p>(b) (6)</p>		<p>(b) (6)</p> <p><u>1 Close Call</u></p> <p>(b) (6)</p> <p>retrieved 2 boxes (4 devices), called pharmacy, then resolved.</p>	<p>(b) (6): assumed each spray was 28 mg so one device would be 56 mg.</p> <p>(b) (6): assumed each spray was 28 mg, so 2 sprays at 28 mg would have provided the complete dose of 56 mg. The HCP noted that having two devices in the box was unusual for her because she would expect the box to have only the number of devices she would need for the patient. In reviewing the patient order before the second trial, she recognized that she should have used a second device and that each device was only 28 mg, not each spray.</p> <p>(b) (6): assumed each spray was 28 mg and there was no indication on the box that the nasal spray device was unusual or that it needed special attention to the instructions, thus it was too much to read quickly while the patient was there.</p> <p><u>Close Call</u></p> <p>(b) (6): box says 28 so it was assumed two boxes were needed. It was mentioned that the box should be clearer or maybe have a color background behind the part on the bottom where it says 28 per device.</p> <p><i>Mitigation strategies:</i></p> <p>No further device design mitigation is possible; only product labeling can influence the HCPs ability to comprehend this instruction. A root cause assessment for the HCPs selecting an incorrect</p>	<p>information presented on the carton is confusing to healthcare providers and lacks clarity to ensure safe and effective use of the product.</p> <p>In the IFU, Step 1-Get ready advises users to confirm the required number of devices. There is an accompanying table, which states that (b) (4) 2 devices contain 56 mg, and 3 devices contain 84 mg.</p> <p>The Applicant proposed only revisions to the carton labeling by increasing the prominence of the total dose for each carton pack. We note that Janssen did not validate the carton labeling revisions.</p> <p>Our review of the carton labeling indicates that the carton labeling could be further improved to indicate the total drug content per spray and total drug content per device. <b><u>We provide specific carton labeling recommendations in Table 4 to address this concern.</u></b> This revision should be incorporated in the user interface and validated in another HF validation study (see section 4.1)</p>
--	---	--	--	---	---

Table 2, specific participants are referred to using an alphanumeric code. The letters preceding each number indicate the group to which the participant belongs:

\*P: patient

HCP: healthcare provider

				number of devices can be traced to the information presented on the carton. On the carton label used in the Human Factors validation study, the prominent information showed the content per device, with information about the unit dosage in smaller font. The Applicant proposes to increase the prominence of the information about the total dose for each carton pack.	
<p><i>Task 4.2</i></p> <p>Patient holds device as shown in IFU</p>	<p>5</p> <p><u>Use Errors</u></p> <p>(b) (6)</p>	<p>1</p> <p><u>Use Difficulty</u></p> <p>(b) (6)</p>	<p><b>Trial 1</b></p> <p>Depressed plunger using palm of hands instead of thumb, as shown in the IFU.</p> <p>(b) (6)</p> <p><b>Trial 2 (Use Difficulty)</b></p> <p>(b) (6): patient did not hold device as shown in IFU but self-corrected before</p>	<p><b>Trial 1</b></p> <p>(b) (6) <b>(Device 1)</b>: HCP said they did not instruct patient on grip because it was important just to get to the tip of the nose, and not hold it a certain way.</p> <p>(b) (6) <b>(Device 2)</b>: HCP and patient both said it does not matter how a nasal spray would get held as long as the spray enters the nose.</p> <p>(b) (6): HCP recognized that the patient held the device differently than recommended by the IFU but did not instruct the patient to do so. The HCP did not instruct the patient because it seemed like he already knew what he was doing.</p> <p>(b) (6) <b>(Devices 1 and 2)</b>: HCP demonstrated the grip indicated in the IFU, but the patient felt that the grip was awkward. Patient indicated that depressing the plunger using her palm allowed her to maintain a better grip of the device and was more comfortable.</p> <p>(b) (6) HCP thought the patient held the device correctly. Patient said he understood the correct way to hold the device but indicated that holding and</p>	<p>The way that the device is held may impact the patient’s ability to depress the plunger and administer the product. Per the DPP medical officer, it may reduce the amount of dose administered.</p> <p>Our review of the IFU notes that the text and accompanying image on how to grip the device are adequately clear.</p> <p>We find the residual risk acceptable. We have no further recommendations at this time.</p>

Table 2, specific participants are referred to using an alphanumeric code. The letters preceding each number indicate the group to which the participant belongs:  
 \*P: patient                      HCP: healthcare provider

			<p>administering first spray</p>	<p>pressing the plunger using his palm felt easier or more comfortable.</p> <p>(b) (6): HCP did not instruct the patient and did not notice the issue.</p> <p><u>Use Difficulty</u></p> <p><b>Trial 2</b></p> <p>(b) (6): Patient was under the impression that the blue finger flange was actually the component of the nasal spray device that moved and not the plunger. While holding the device with her thumb and pointer finger on the flange and the device plunger resting on her ring finger, the patient struggled to actuate the device and changed her hand positioning to the proper configuration, which allowed her to administer the spray. Patient had not been told by the HCP how the device worked, and she has experience with other nasal spray devices, so her initial confusion about how the device worked was based on an assumption of how other nasal spray devices she has used have worked.</p> <p><i>Mitigation strategies:</i></p> <p>Note that there is no additional device or IFU design enhancements that can further influence users to position the device in the recommended manner; potential use-related hazards have been mitigated to the greatest possible extent.</p>	
--	--	--	----------------------------------	---	--

Table 2, specific participants are referred to using an alphanumeric code. The letters preceding each number indicate the group to which the participant belongs:  
 \*P: patient                      HCP: healthcare provider

				<p>The number of use errors decreased from 5 to 0 between Trials 1 and 2, demonstrating that as HCPs become familiar with this therapy through repeated use throughout the initial and maintenance dosing periods, the recommendations for head and hand positions will become more common knowledge.</p>	
<p><i>Subtask 5.3a</i> Patient pushes plunger all the way up until it stops</p>	<p><u>Use Difficulty</u></p> <p>1 (b) (6)</p>	<p><u>Use Error</u></p> <p>1 (b) (6)</p>	<p><b>Trial 1</b> (b) (6) Struggled to depress plunger but was able to resolve with different hand position.</p> <p><b>Trial 2</b> (b) (6): Patient delivered 2 sprays into first nostril</p>	<p><u>Use Difficulty</u></p> <p><b>Trial 1</b> (b) (6): Patient indicated that trying to depress the plunger with her original grip and with her left (non-dominant) hand was awkward. Patient was able to fully depress the plunger once she adjusted her grip on the device.</p> <p><u>Use Error</u></p> <p><b>Trial 2</b> (b) (6) Patient said the device feedback led her to think she had only delivered 1 spray.</p> <p><i>Mitigation strategies:</i></p> <p>The error rate is accepted as residual risk. As a mitigation for the close call that occurred in Trial 1, the HCP can direct patients to use their dominant hand with no impact on device performance. As a mitigation for the use error in Trial 2, the visual indicator clearly depicts whether one or two sprays have been delivered; no further design mitigation is feasible.</p>	<p>The potential harm associated with not pushing the plunger all the way up is dose omission. In some cases, difficulty with plunger depression will lead to the need for the patient to perform multiple actuations to deliver 2 sprays from the device if they recognize that they did not receive the full dose.</p> <p>We note that in one response the patient indicated that the device feedback led her to think she had only delivered one spray. However, the sponsor did not provide further root cause information to better elucidate what exactly about the feedback led to this belief by the patient, so it is unclear how the feedback mechanism may be improved. We note that the feedback mechanism includes an indicator that is intended to convey when the sprays have been administered and our expert and heuristic review did not identify further areas for improvement with this feature.</p> <p>We also confirmed with CDRH that the actuation performance test results are</p>

Table 2, specific participants are referred to using an alphanumeric code. The letters preceding each number indicate the group to which the participant belongs:

\*P: patient

HCP: healthcare provider

					adequate for this population and were tested on the most current device design.  We find the residual risk acceptable. We have no further recommendations at this time.
<p><b>Task 6.2</b></p> <p>Patient repeats subtasks 5.1-5.4 spraying into the opposite nostril</p>	<p><u>Use Errors</u></p> <p>3</p>	<p><u>Use Error</u></p> <p>1</p>	<p><b>Trial 1</b></p> <p>Patient administered both sprays into same nostril</p> <p>(b) (6)</p> <p><b>Trial 2</b></p> <p>(b) (6)</p> <ul style="list-style-type: none"> <li>- Patient did not change nostrils</li> <li>- Patient administered medication from Device 2 entirely in opposite nostril to balance having taken complete</li> </ul>	<p><b>Trial 1</b></p> <p>(b) (6): HCP instructed a second spray into the same nostril; when probed she said the IFU seems clear and there was nothing to fix, but she was nervous the first time.</p> <p>(b) (6): Patient administered both sprays from first device into the same nostril per instruction of the HCP. HCP indicated that she was focused more on ensuring the total mg dose was administered per nostril and that she did not focus on the instructions to alternate nostrils per spray of a given device.</p> <p>(b) (6): The patient said the IFU was not clear on how to administer the 56 mg dose using 2 devices. The HCP interpreted the IFU to mean that medication should be administered into one nostril (in totality-28 mg) first and then administered into the opposite nostril (in totality-28 mg).</p> <p><b>Trial 2</b></p> <p>(b) (6): Patient thought she only pressed once and thought the device may have malfunctioned. In addition, the nurse explained that the sequence of</p>	<p>The clinical impact of receiving a second spray in the same nostril is that the patient may potentially receive less than the intended dose (because not all the drug may be absorbed in the mucosa or some may leak out of the nostril) and may not realize the full effect of the treatment.</p> <p>Our review of the IFU finds that Step 4 advises, the user to “Repeat Step 4 to deliver second spray.”</p> <p>In the validation study, patients sprayed both sprays into the same nostril because the HCP advised them to. One HCP misinterpreted how to administer the 56 mg dosing using 2 devices. Another HCP did not explain the sequence of administration to the patient. We note that Step 4 in the IFU indicates “Switch hands to insert tip into the second nostril. Repeat Step 4 to deliver second spray.”</p>

Table 2, specific participants are referred to using an alphanumeric code. The letters preceding each number indicate the group to which the participant belongs:

\*P: patient

HCP: healthcare provider

			<p>first dose into original nostril.</p>	<p>administration did not seem important, so the way to recover from an accidental delivery of 2 sprays into the first nostril would be to deliver 2 sprays into the other nostril.</p> <p><i>Mitigation strategies:</i></p> <p>The number of use errors (“I”) decreased from 3 to 1 between Trials 1 and 2, demonstrating that as HCPs become familiar with this therapy through repeated use throughout the initial and maintenance dosing periods, the instructions provided in the IFU will become more common knowledge. The reduced error rate is accepted as residual risk as no additional modifications to eliminate these use errors completely are reasonably feasible.</p>	<p>The Applicant proposes no mitigation strategy for the IFU.</p> <p>Based on the root cause analysis information and subjective feedback received, we recommend that the statement, “Instruct patients to alternate nostrils for each spray until the complete dose has been administered.” be included in the Step 4 of the IFU. This may help to minimize the risk for this instruction being overlooked or not carried out.</p> <p><b><u>We provide specific IFU recommendations in Table 4 of the review to address our concern.</u></b> This revision should be incorporated in the user interface and validated in another HF validation study (see section 4.1).</p>
<p><i>Task 7.1-7.2</i></p> <p>HCP takes device from patient and checks that no green dots are showing</p>	<p><u>Use Errors</u></p> <p>2</p>	<p>0</p>	<p><b>Trial 1</b></p> <p>(b) (6): Threw device into the garbage after use by patient, then self-corrected and checked that no green dots remained on the device.</p>	<p><b>Trial 1</b></p> <p>(b) (6): Need to check for green dots is not fully apparent.</p> <p>(b) (6): HCP said there are lot of directions to remember. However, the HCP still directed the patient to spray twice, thus the full contents of the device were successfully delivered.</p> <p><i>Mitigation strategies:</i></p>	<p>The potential harm associated with not checking the device after administration is that an underdose may not be identified.</p> <p>We note that Step 5 advises the HCP to, “Take device from patient. Check that indicator shows <b>no green dots.</b>”</p> <p>The Applicant did not propose a mitigation strategy. We recommend bringing</p>

Table 2, specific participants are referred to using an alphanumeric code. The letters preceding each number indicate the group to which the participant belongs:

\*P: patient

HCP: healthcare provider



				<p>never had a nasal spray system that has two devices needed. She said the box should say 56 mg or 28 x 2.</p> <p>(b) (6): HCP assumed each spray was 28 mg and said there was no indication on the box that the nasal spray device was unusual or that it needed special attention to the instructions. The HCP also mentioned that it was too much to read quickly while the patient was there.</p> <p><i>Mitigation strategies:</i></p> <p>The number of use errors (“I”) decreased from 5 to 0 between Trials 1 and 2, demonstrating that as HCPs become familiar with this therapy through repeated use throughout the initial and maintenance dosing periods, the instructions provided in the IFU will become more common knowledge.</p> <p>No further device design mitigation is possible; only the product labeling can influence the HCP’s ability to comprehend this instruction. As an additional mitigation, the carton label has been redesigned to more clearly communicate the total dose for each carton pack. The redesigned label makes the choice of the number of devices needed to deliver the prescribed dose self-evident.</p>	
--	--	--	--	--	--

Table 2, specific participants are referred to using an alphanumeric code. The letters preceding each number indicate the group to which the participant belongs:  
 \*P: patient                      HCP: healthcare provider

### 3.2. ANALYSIS OF ESSENTIAL /NON-CRITICAL TASKS

We observed use errors/close calls/use difficulties with the following essential tasks:

#### HCP checks expiration date

We note that four (4) healthcare providers in Trial 1 did not check the expiration date prior to proceeding with the administration process. We note this type of failures are not unique to the use of this product. We evaluated the subjective feedback from the participants that made these use errors. Several participants attributed these errors failures to expecting medication that they just received from the pharmacy to not be expired or they were not used to checking their own expiration dates. Our review of the container labels identified that the expiration is prominently noted on the side display panel. We find the residual risk acceptable and do not have any recommendations at this time.

#### HCP peels blister and remove device

We note that four (4) HCP in Trial 1 and one (1) HCP in Trial 2 let the patient peel the blister and remove the device even though this task is characterized as one that the HCP should complete. Although the IFU mentions that the HCP peels blister and removes the device, this product is administered under supervision of a healthcare professional, and the task of removing the peel blister and device is unlikely to lead to harm if completed by the patient. We find the residual risk acceptable and do not have any recommendations at this time.

#### Patient reclines or tilts head

We note one (1) patient in Trial 1 did not recline or tilt their head. We evaluated the subjective feedback from the participants that made these use errors. The patient attributed the failure to the HCP did not instruct the patient because they forgot. Per the medical officer, the potential harm associated with the patient not reclining or tilting head is minimal leakage of the liquid drug from the nose, which would not result in a clinically relevant loss of drug to the patient. As such, we find the residual risk acceptable and have no recommendations at this time.

#### Patient inserts tip until nose rest touches the skin between nostrils

We note three (3) patients in Trial 1 and one (1) patient in Trial 2 incorrectly oriented the device and nose rest. We evaluated the subjective feedback from the participants that made these use errors. Participants attributed these errors to feeling uncomfortable in the correct orientation, believing the nose rest could rest against other parts of the exterior nostril, or believing the device was usable in different orientations. The potential harm of not inserting the nasal spray tip on the nose rest as instructed in the IFU is minimal leakage of the liquid drug from the nose, which would

not result in a clinically relevant loss of drug to the patient. Our review of the labels and labeling did not identify any vulnerabilities related to the failure reported with this task. As such, we find the residual risk acceptable and have no recommendations at this time.

#### Patient closes opposite nostril

We note seven (7) patients in Trial 1 and one (1) patient in Trial 2 did not close the opposite nostril. We evaluated the subjective feedback from the participants that made these use errors. Participants attributed these errors to the HCP not instructing them to close the opposite because they forgot or did not follow the IFU. Per the DPP medical officer, this may reduce the amount of dose administered, probably to a minor extent. Our review of the IFU determined that the IFU clearly indicates to close the opposite nostril during administration. We find the residual risk acceptable and have no recommendations at this time.

#### Patient breathes in through nose

We note two (2) patients in Trial 1 did not breath in through the nose during self-administration. We evaluated the subjective feedback from the participants that made these use errors. Participants attributed these errors to the HCP not instructing them to breath in through the nose. Per the DPP medical officer, may reduce the amount of dose administered, probably to a minor extent. We note that the IFU clearly indicates in bold font, **“Breathe in through nose.”** In addition, there is an accompanying illustration demonstrating the step. We find the IFU is adequately clear. We find the residual risk acceptable and have no recommendations at this time.

#### Patient sniffs gently after spraying

We note one (1) patient in Trial 1 and one (1) patient in Trial 2 did not sniff gently after spraying. We evaluated the subjective feedback from the participants that made these use errors. Participants attributed these errors to the HCP not instructing them to do so. One (1) HCP did not instruct the patient because he was used to nasal sprays that do not require sniffing. The other HCP did not mention this step saying he thought the patient would remember it from prior use and that there is no way to verify that a patient does this step. Per the DPP medical officer, this may reduce the amount of dose administered, probably to a minor extent. In the IFU is the statement in bold font, <sup>(b) (4)</sup> **“Sniff gently** after spraying to keep medication inside nose.” In addition, there is an accompanying illustration demonstrating the step. We find the IFU is adequately clear. We find the residual risk acceptable and have no recommendations at this time.

#### Patient holds device in opposite hand

We note five (5) patients had failures and one (1) patient had difficulty holding the device in the opposite hand in Trial 1. There was one (1) patient in Trial 2 who held the device in her dominant hand during use of both devices. We evaluated the subjective feedback from the participants that made these use errors and difficulties. Participants attributed these errors to the HCP not instructing them to switch hands or they felt more comfortable using the more dominant hand. Observation and interview data indicates that patients were generally able to deliver both sprays into the nasal cavity regardless of whether the dominant or less dominant hand was utilized, and patient reported that they did not think that not switching hands impacted their ability to deliver both sprays. We find the residual risk acceptable and have no recommendations at this time.

#### Patient rests for 5 minutes

We note two (2) patients had failures in Trial 1 and one (1) patient had a failure in Trial 2. We evaluated the subjective feedback from the participants that made these use errors. Participants attributed these errors to assuming the 5 minutes was not necessary, missed the instruction in the IFU, or misunderstood IFU description of 2 sprays to mean 2 devices. Per the DPP medical officer, this may reduce the amount of dose administered, probably to a minor extent. Our review of the labels and labeling found the instruction adequately clear. We find the residual risk acceptable and have no recommendations at this time.

### **3.3. LABELS AND LABELING**

We identified concerns with the labels and labeling from a medication error perspective below in Table 3 for the division and Table 4 for the Applicant. The tables include the identified medication error issues with the submitted labels and labeling and packaging, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. We have focused on recommendations for the single device carton packaging configuration because DPP informed DMEPA that they intend to ask Janssen to market a single packaging configuration of one device in one carton.

### **3.4. ASSESSMENT OF PACKAGING**

The Applicant proposes the product be supplied in a carton containing one 28 mg nasal spray device (28 mg total dose), a carton containing two 28 mg nasal spray devices (56 mg total dose), and a carton containing three 28 mg nasal spray devices (84 mg total dose). Based on the HF data submitted, confusion can occur between the three proposed packages regarding strength and dosing. Additionally, the proposed packaging may contribute to product selection medication errors and potential wrong dose errors. Based on the results

of the HF validation study, it was not clear to users that the number of devices per carton is dose specific. Confusion by HCPs was cited regarding how much drug is available per spray and how much drug is available per device.

DPP informed DMEPA that they intend to ask Janssen to market a single packaging configuration of one device in one carton. Marketing with only a single packaging configuration of one device per carton may help to address potential use errors that may arise due to confusion between the three packaging presentations and minimize the risk for selection errors. However, with a single packaging configuration, the risk may still arise for underdose errors if a user (e.g., a nurse in the clinic) does not realize that he/she should administer the contents of more than one device to achieve the intended dose. A risk for overdose errors may also arise if there is a single packaging configuration and a user administers more than the required number of devices (2 or 3) to achieve the intended dose when only a one single device is required. Thus, regardless of the number of packaging configurations, information regarding the contents per spray and per device must be clarified to minimize the risk for medication error. Additional, clarification is also needed to better inform providers on how many sprays and how many devices are needed to achieve each intended dose.

The Applicant proposed revisions to the strength statement on the carton labeling but has not provided data to demonstrate that the proposed mitigations are effective and do not introduce new use-related risks. Since the Applicant's proposed revisions to the carton labeling have not been tested in the HF validation study, we do not have data to support that these changes will mitigate the errors shown in the HF validation study. Overall, we have found the residual risk unacceptable based on the results of the HF study, thus the Applicant should implement further risk mitigation strategies then validate them in another study.

Moving forward, if a single packaging configuration of one device packaged in one carton is what will be pursued, we recommend that the Applicant tests a single device per package configuration in the study and assess whether healthcare providers can select the correct number of devices to obtain a specified dose.

**Table 3: Identified Issues and Recommendations for Division of Psychiatry Products**

	<b>Identified Issue</b>	<b>Rationale for Concern</b>	<b>Recommendation</b>
<b>Highlights of Prescribing Information (HPI)</b>			
1.	The dosage information, as presented in the table in the Dosage and Administration section, is confusing due to the layout and the abbreviated manner in which the information is presented.	Lack of clarity may lead to underdose or overdose medication errors.	We recommend the Applicant revise the table and consider the following or use other methods to clarify the information: <ul style="list-style-type: none"><li>• Move the Maintenance Phase dosing information so that it is positioned below the Induction Phase information</li><li>• Remove the dosage information for patients 65 years and older out of the footnote and place it inside the table.</li></ul>
<b>Full Prescribing Information (FPI)</b>			
1.	The dosage information, as presented in Table 1 in Section 2.1 Dosage – Adults, is confusing due to the layout and the abbreviated manner in which the information is presented.	Lack of clarity may lead to underdose or overdose medication errors.	We recommend the Applicant revise the table and consider the following or use other methods to clarify the information: <ul style="list-style-type: none"><li>• Move the Maintenance Phase dosing information so that it is positioned below the Induction Phase information</li><li>• Remove the dosage information for patients 65 years and older out of the footnote and place it inside the table.</li></ul>

**Table 4: Identified Issues and Recommendations for Janssen (entire table to be conveyed to Applicant)**

	Identified Issue	Rationale for Concern	Recommendation
<b>Instructions for Use (IFU)</b>			
1.	The instruction for the patient to blow their nose before first device use only is important information and may be overlooked.	Step 1 of the IFU instructs the user to “Get ready” and HCPs are advised before first device only: <b>instruct patient to blow nose before first device only</b> and confirm required number of devices. We note failures in the HF validation study included participant performance and subjective feedback regarding overlooking this step and one HCP recommended relocating the instruction to the section, “Prepare patient” as this was pertaining to the patient.	We recommend that the first image and instruction in Step 3 “Prepare Patient” should be instructing the “...patient to blow nose before first device only.” This may help to minimize the risk for this instruction being overlooked or not carried out.
2.	The instruction for the HCP to take the device from the patient and check that no green dots are showing is important information and may be overlooked.	Step 5 of the IFU instructs the user to, “Take device from patient. Check that indicator shows <b>no green dots.</b> ” We note failures in the HF validation study included participant performance and subjective feedback regarding the need to check for the green dots was not fully apparent.	We recommend revising the statement in bold font, “ <b>Check that indicator shows no green dots.</b> ” to help bring additional prominence to this instruction.
3.	The instruction for the patient to repeat the administration in alternating nostrils	Step 4 of the IFU instructs the user to, <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span> Switch hands to insert tip into the <b>second nostril</b> . Repeat Step 4 to deliver second spray.” We note failures in	We recommend including the statement in Step 4, “Instruct patients to alternate nostrils for each spray until the complete dose has been

	until the complete dose is administered is important information and may overlooked.	the HF validation study included participant performance and subjective feedback regarding the IFU not being clear if the total contents from one device should be administered in the same nostril.	administered.” to minimize the risk for this instruction to be overlooked.
4..	The sub steps are not indented, numbered, bulleted or otherwise formatted for improved readability of the text.	Some of the sub steps may be overlooked without improved formatting of the text.	Consider the use of bulleting in order to improve the readability of the sub steps. As an example, consider the following bulleted format for Step 2:

(b) (4)

--	--	--	--

**Comments for the Container Label, Blister Label, and Single Device Carton Labeling**

1.	The established name does not appear to be	Lack of sufficient prominence of the established name may contribute to product selection medication errors.	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
----	--	--	---

	at least ½ the size of the proprietary name.		
2.	As currently presented, the statement of strength is confusing because it does not state the number of milligrams delivered per spray or the number of sprays delivered by the device.	The statement of strength is confusing and may contribute to wrong dose medication errors.	Revise the statement of strength to include the number of milligrams delivered per spray and the number of sprays delivered by the device, as follows:  <b>14 mg esketamine per spray</b>  <b>Device delivers 2 sprays (28 mg esketamine)</b>
3.	The proposed expiration date format is not indicated.	The proposed format for the expiration date is requested in order that we may determine whether it may be confusing and lead to deteriorated drug medication errors.	Indicate the proposed expiration date format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen

			or a space be used to separate the portions of the expiration date.
<b>Packaging</b>			
1.	Your currently proposed packaging (i.e., cartons containing 1, 2, or 3 devices) may be confusing because it may not be clear which package should be selected for a particular dose or that all of the devices in a particular package should be used.	<p>The proposed packaging may contribute to product selection medication errors and potential wrong dose errors.</p> <p>Based on the results from your HF validation study, it was unclear to users that the number of devices per carton is dose specific. There is also a risk that if the dose specific carton needed is not on hand, an individual device(s) may be removed from a multidevice carton, which may lead to further confusion.</p>	Consider marketing a single package configuration for your product (i.e., one device per carton). This may help to minimize potential product selection errors. We recommend that you conduct another HF validation study and use a single device per package configuration in the study. Also, the study should assess whether healthcare providers can select the correct number of devices to obtain for a specified dose.

## **4 CONCLUSION & RECOMMENDATIONS**

The results of the HF validation study did not demonstrate that the user interface supports the safe and effective use of this product, and the Applicant implemented revisions to the user interface without providing additional validation data to demonstrate effectiveness of the revisions.

Furthermore, our evaluation of the proposed user interface, proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 3 for the Division and Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to the Applicant. In addition, we provide our recommendations for the Applicant related to the HF validation study in section 4.1 below. We recommend that the Applicant consider additional user interface design modifications to the single package configuration to further mitigate residual risk and implement our recommendations prior to validating these revisions in another HF validation study.

### **4.1. RECOMMENDATIONS FOR JANSSEN**

Your human factors (HF) validation study results did not demonstrate that your proposed product can be used safely and effectively by the intended users for its intended uses and use environments. You determined that no tasks were critical for the use of your product; however, we disagree with your determination since failure to receive the intended dose would compromise medical care as the patient would not receive the intended benefit from their prescribed therapy. Thus, your HF study results identified several use errors and close calls that occurred on critical tasks. Additionally, you have not provided data to demonstrate that your proposed labeling mitigations are effective and do not introduce new use-related risks. Our review indicates that additional risk mitigations are necessary, and therefore, another HF validation study should be conducted to demonstrate the effectiveness of additional risks mitigations that are implemented. Furthermore, based on our evaluation, we have identified areas in the product labels and labeling that require revisions to optimize your product user interface and minimize the risk for medication errors. Please see our table which contains our recommendations. We recommend that our recommendations, in addition to any additional risk mitigation strategies you may apply, are implemented for the product user interface and validated as part of the HF validation study that you conduct.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 5 presents relevant product information for Spravato that Janssen Pharmaceuticals, Inc. submitted on September 4, 2018 and November 20, 2018.

<b>Table 5. Relevant Product Information for Spravato</b>													
<b>Initial Approval Date</b>	N/A												
<b>Active Ingredient</b>	Esketamine												
<b>Indication</b>	For treatment-resistant depression (b) (4) [Redacted]												
<b>Route of Administration</b>	Intranasal												
<b>Dosage Form</b>	Nasal Spray												
<b>Strength</b>	28 mg per device (equivalent to 32.3 mg esketamine hydrochloride)												
<b>Dose and Frequency</b>	<p>Spravato should be administered in conjunction with an oral antidepressant. Dose adjustments should be made based on efficacy and tolerability to the previous dose.</p> <table border="1"> <thead> <tr> <th><b>Induction Phase</b></th> <th><b>Maintenance Phase</b></th> </tr> </thead> <tbody> <tr> <td>Weeks 1-4 (two treatment sessions/week):</td> <td><b>Weeks 5-8:</b></td> </tr> <tr> <td>Starting Day 1 dose*: 56 mg</td> <td>56 mg or 84 mg once weekly</td> </tr> <tr> <td>Subsequent doses: 56 mg or 84 mg</td> <td><b>From Week 9:</b></td> </tr> <tr> <td></td> <td>56 mg or 84 mg every 2 weeks or once weekly**</td> </tr> <tr> <td>Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.</td> <td>Periodically reexamine the need for continued treatment.</td> </tr> </tbody> </table> <p>* For patients ≥65 years Day 1 starting dose is 28 mg ** Dosing frequency should be individualized to the lowest frequency to maintain remission/response.</p>	<b>Induction Phase</b>	<b>Maintenance Phase</b>	Weeks 1-4 (two treatment sessions/week):	<b>Weeks 5-8:</b>	Starting Day 1 dose*: 56 mg	56 mg or 84 mg once weekly	Subsequent doses: 56 mg or 84 mg	<b>From Week 9:</b>		56 mg or 84 mg 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.	Periodically reexamine the need for continued treatment.
<b>Induction Phase</b>	<b>Maintenance Phase</b>												
Weeks 1-4 (two treatment sessions/week):	<b>Weeks 5-8:</b>												
Starting Day 1 dose*: 56 mg	56 mg or 84 mg once weekly												
Subsequent doses: 56 mg or 84 mg	<b>From Week 9:</b>												
	56 mg or 84 mg 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.	Periodically reexamine the need for continued treatment.												
<b>How Supplied</b>	<p>Spravato is available as an aqueous solution of esketamine hydrochloride within a single-use nasal spray device. The device delivers two sprays, one spray into each nostril. The total volume of drug product per device to be delivered is 0.2 mL containing a total of 32.3 mg of esketamine hydrochloride (equivalent to 28 mg of esketamine).</p> <p>Spravato Nasal Spray 28 mg is provided in a single-use nasal spray device packaged in a sealed blister.</p> <p>Spravato is available in the following presentations:</p>												

	<ul style="list-style-type: none"> <li>• Carton containing one 28 mg nasal spray device (28 mg total dose)</li> <li>• Carton containing two 28 mg nasal spray devices (56 mg total dose)</li> <li>• Carton containing three 28 mg nasal spray devices (84 mg total dose)</li> </ul> <p>Within each pack, each device is individually packaged in a sealed blister.</p>
<b>Storage</b>	Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]
<b>Intended User Groups</b>	<ul style="list-style-type: none"> <li>• Patients diagnosed with major depressive disorder (MDD), 18+ years of age</li> <li>• Healthcare providers (nurses and psychiatrists), 18+ years of age, who regularly treat and administer medication to patients diagnosed with depression.</li> </ul>
<b>Intended Use Environment(s)</b>	Hospital or clinic under the supervision of a healthcare provider (HCP)

## **APPENDIX B. BACKGROUND INFORMATION**

### **B.1 PREVIOUS HF REVIEWS**

#### **B.1.1 Methods**

On December 20, 2018, we searched the L:drive and AIMS using the terms, Esketamine to identify reviews previously performed by DMEPA.

#### **B.1.2 Results**

Our search identified one previous review<sup>b</sup> pertinent to this review, and we confirmed that our previous recommendations were implemented.

## **APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS**

The background information can be accessible in EDR via:

<\\cdsesub1\evsprod\nda211243\0001\m3\32-body-data\32r-reg-info\medical-device.pdf>

## **APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT**

The HF study results report can be accessible in EDR via:

<\\cdsesub1\evsprod\nda211243\0001\m3\32-body-data\32r-reg-info\medical-device-hfv-ds-tec-127301.pdf>

## **APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW**

In a November 16, 2018 Information Request, we requested that the Applicant submit intend-to-market product samples to assist in completion of our review of the carton labeling and container labels. The Applicant submitted the product samples. The Applicant submitted their response on November 20, 2018.

In a November 27, 2018 Information Request, we requested that the Applicant provide their nasal spray HF validation study results in a tabular format. The Applicant submitted their response on November 29, 2018.

<\\cdsesub1\evsprod\nda211243\0022\m1\us\response-to-fda-27nov2018.pdf>

---

<sup>b</sup> Holmes, L. Human Factors Protocol Review for Esketamine IND 114345. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 19. RCM No.: 2016-1230.

## APPENDIX F. LABELS AND LABELING

### E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>c</sup> along with postmarket medication error data, we reviewed the following Spravato labels and labeling submitted by Janssen Pharmaceuticals, Inc. on September 4, 2018.

- Container Label
- Blister Label
- Carton Labeling
- Instructions for Use (image not shown), accessible at:  
<\\cdsesub1\evsprod\nda211243\0001\m1\us\draft-label-text-spravato-28mg-device-np-sol-ifu-pic.pdf>
- Prescribing Information (Image not shown), accessible at:  
<\\cdsesub1\evsprod\nda211243\0001\m1\us\draft-labeling-text.pdf>

---

<sup>c</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

**G.2 Label and Labeling Images (not to scale)**

**Bottle Label**



**Blister Label**



3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

LORETTA HOLMES  
01/14/2019 01:28:52 PM

NICOLE B GARRISON  
01/14/2019 01:47:33 PM

TERESA S MCMILLAN  
01/14/2019 02:24:48 PM

IRENE Z CHAN  
01/14/2019 03:18:30 PM