Real-World Safety Profile of Esketamine Nasal Spray During the First 12 Treatment Sessions: An Analysis at 58 Months After Approval in the United States

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Introduction

- Esketamine nasal spray (ESK) was approved by the US Food and Drug Administration, in conjunction with an oral antidepressant, in March 2019 for the treatment of treatment-resistant depression (TRD) in adults and in July 2020 for the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior[1]
- The recommended ESK dosing for TRD is shown in **Table 1**

TABLE 1: Recommended ESK dosing for TRD

Treatment Phase	Administration	Adult dosing
Induction phase		
Weeks 1-4: sessions 1-8	Twice weekly	Day 1 starting dose: 56 mg Subsequent doses: 56 or 84 mg
Maintenance phase		
Weeks 5-8 (early maintenance): sessions 9-12	Once weekly	56 or 84 mg
Week 9 and later: sessions 13 and beyond	Every 2 weeks or once weekly[a]	56 or 84 mg

ESK, esketamine nasal spray; TRD, treatment-resistant depression.
[a]Dosing frequency should be individualized to the least-frequent dosing to maintain remission/response.

- Based on FDA requirements, Janssen developed and implemented a Risk Evaluation and Mitigation Strategy (REMS) program at the time of approval to mitigate the risks of serious adverse outcomes, including those resulting from sedation, dissociation, or from misuse and abuse, by ensuring the following
  - Healthcare settings (HCSs) that treat patients and pharmacies that dispense ESK are REMS certified
  - ESK is only dispensed and administered to patients in a medically supervised HCS that monitors these patients
  - Outpatients are enrolled in the REMS registry prior to treatment with ESK to further characterize risks and support safe use
  - All patients are informed about the potential for serious adverse outcomes resulting from sedation and dissociation and the need for monitoring
  - Patient administration is performed under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider in a healthcare setting for at least 2 hours after dosing for resolution of sedation and dissociation, and changes in vital signs
  - ESK is never dispensed directly to patients for home use
- To comply with the REMS, certified pharmacies and HCSs must follow specific requirements to receive, dispense, and treat patients with ESK (**Table 2**)

Objective

- To examine and summarize real-world incidence of ESK treatment-emergent adverse events (TEAEs) of interest (i.e., actively solicited reports of sedation, dissociation, and increased blood pressure [BP]) and serious adverse events (SAEs) and to determine if the incidence of these events change between the induction and maintenance periods

Methods

- Data from ESK REMS patient monitoring forms were evaluated to describe the key safety findings for the first 58 months (March 5, 2019, to January 5, 2024) after US product approval, with a focus on ESK TEAEs of interest (sedation, dissociation, and increased BP) and SAEs during the first 12 treatment sessions
- Results were summarized by first treatment session, sessions 1-8 (induction phase), and sessions 9-12 (early maintenance phase); the first 12 ESK treatment sessions were chosen for this analysis because most patients would have received ESK on similar schedules up to this point
  - TEAE rates reflect the percentage of patients who experienced ≥1 TEAE during the treatment phase
- Details of each outpatient treatment session, including the duration of monitoring after administration, BP values, TEAEs of interest (i.e., sedation and dissociation), and all SAEs observed, are documented in the REMS patient monitoring form, which is required to be submitted to the REMS administrator within 7 days after ESK administration. Healthcare providers in the outpatient setting are asked through solicited reporting to specifically record whether sedation, dissociation, and/or increased BP occurred at each treatment session
  - Post-administration BP increase, as measured at 40 min after dosing or at the time of discharge, was defined as BP post-administration increase of ≥20 mm Hg to a value ≥180 mm Hg for systolic pressure and/or ≥15 mm Hg to a value ≥105 mm Hg for diastolic pressure compared with values prior to administration
  - If pre-administration BP values were missing, systolic values ≥180 mm Hg and/or diastolic values ≥105 mm Hg after administration were also considered an increase
- SAEs for the ESK REMS were determined by the reporter and defined as any event occurring during or between sessions that results in
  - Hospitalization
  - Disability or permanent damage
  - Death
  - A life-threatening event
  - An important medical event (defined as any event that may jeopardize the patient or may require intervention to prevent any of the above outcomes)

TABLE 2: ESK REMS certification requirements for HCSs and pharmacies

	Outpatient HCSs	Inpatient HCSs	Pharmacies
Designate an authorized representative to review the ESK prescribing information and REMS Program Overview, complete an enrollment form and submit it to the REMS, and oversee implementation and coordinate activities of the REMS	X	X	X
Train all relevant staff involved in prescribing, dispensing, and/or administering ESK	X	X	X
Create processes and procedures to ensure ESK is administered under the direct supervision of a healthcare provider followed by at least 2 hours of monitoring	X	X	
Create processes and procedures to ensure ESK is dispensed only to REMS-certified HCSs and never directly to a patient			X
Submit all required patient enrollment and monitoring forms within the required time frames	X		
Maintain all records of product received and dispensing information	X	X	X
Comply with all REMS audits	X	X	X

ESK, esketamine nasal spray; HCS, healthcare setting; REMS, Risk Evaluation and Mitigation Strategy program. See enrollment form for a full list of requirements.

Results

Baseline patient characteristics

- A total of 58,483 patients had ≥1 ESK treatment session during the evaluation period. At the first treatment session, most patients (65.2%) were aged between 18 and 49 years, and 61.1% were female (**Table 3**)

TABLE 3: Patients with ≥1 ESK treatment session (March 5, 2019, to January 5, 2024)

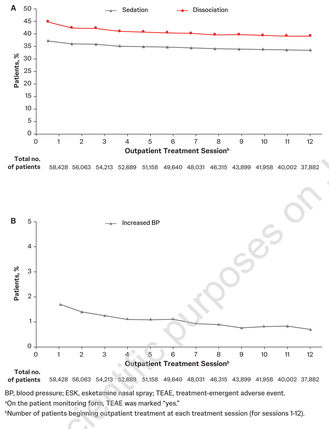
n (%)	Patients with ≥1 ESK treatment session N = 58,483
Sex	
Female	35,762 (61.1)
Male	22,300 (38.1)
Other/unknown	421 (0.7)
Age category	
≤12 years[a]	1 (<0.1)
13-17 years[a]	55 (0.1)
18-29 years	11,758 (20.1)
30-39 years	13,577 (23.2)
40-49 years	12,774 (21.8)
50-59 years	10,895 (18.6)
60-64 years	4132 (7.1)
65-74 years	4359 (7.5)
≥75 years	932 (1.6)
Region[b]	
Southern United States	20,844 (35.6)
Western United States	14,453 (24.7)
Midwestern United States	13,896 (23.8)
Northeastern United States	9272 (15.9)
Other/unknown	18 (<0.1)

ESK, esketamine nasal spray.
[a]ESK is not approved for use in patients <18 years of age.
[b]According to 2010 US Census Bureau Geography Division guidelines.

TEAEs of sedation, dissociation, and increased BP

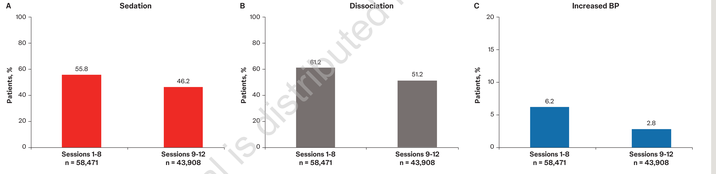
- Rates of TEAEs of sedation, dissociation, and increased BP showed a consistent trend over the course of treatment (**Figure 1**)
- Cumulative rates of solicited ESK TEAEs of interest in sessions 1-8 and sessions 9-12 were 55.8% and 46.2% for sedation, 61.2% and 51.2% for dissociation, and 6.2% and 2.8% for increased BP, respectively. Rates of TEAEs of interest generally decreased from induction to early maintenance (**Figure 2**)

FIGURE 1: Incidence of solicited[a] reports of ESK TEAEs of interest over each of the first 12 treatment sessions: (A) sedation and dissociation and (B) increased BP



BP, blood pressure; ESK, esketamine nasal spray; TEAE, treatment-emergent adverse event.
[a]On the patient monitoring form, TEAE was marked "yes."
[b]Number of patients beginning outpatient treatment at each treatment session (for sessions 1-12).

FIGURE 2: Cumulative incidence of solicited[a] ESK TEAEs of interest by treatment phase: (A) sedation, (B) dissociation, and (C) increased BP



BP, blood pressure; ESK, esketamine nasal spray; TEAE, treatment-emergent adverse events.
For sessions 1-8, n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment sessions 1 and 8 (these data are inclusive of the first treatment session).
For sessions 9-12, n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment sessions 9 and 12 (inclusive).
[a]On the patient monitoring form, TEAE was marked "yes."

- Rates of sedation, dissociation, and increased BP decreased from the induction phase to the early maintenance phase across all dose levels (**Table 4**)

TABLE 4: TEAEs of interest by dose level and treatment session

n (%)	Sessions 1-8		Sessions 9-12	
	Last session dose[a]		Last session dose[a]	
	56 mg n = 11,477	84 mg n = 46,397	56 mg n = 4073	84 mg n = 39,505
Sedation[b]	5864 (51.1)	26,385 (56.9)	1768 (43.4)	18,336 (46.4)
Dissociation[c]	6207 (54.1)	29,153 (62.8)	1732 (42.5)	20,543 (52.0)
Increased BP[d]	706 (6.2)	2886 (6.2)	126 (3.1)	1095 (2.8)

BP, blood pressure; TEAE, treatment-emergent adverse event.
Patients in the full analysis set had ≥1 treatment session.
[a]Last session with any dose.
[b]On the patient monitoring form, sedation was marked "yes."
[c]On the patient monitoring form, dissociation was marked "yes."
[d]A BP increase at 40 min or at the time of discharge was defined as post-administration BP increased ≥20 mm Hg to a value ≥180 mm Hg for systolic pressure or ≥15 mm Hg to a value ≥105 mm Hg for diastolic pressure compared with values prior to administration. If pre-administration blood pressure was missing, systolic values ≥180 mm Hg or diastolic values ≥105 mm Hg at 40 min after administration were also considered an increase.

SAEs of sedation, dissociation, and increased BP

- At first treatment session, sessions 1-8, and sessions 9-12, SAE reports of sedation, dissociation, and increased BP were present in ≤0.1% of patients treated (**Table 5**)
- During the first 12 treatment sessions, the most common SAEs were dissociation, dizziness, hypertension, increased BP, nausea, and vomiting (each 0.1%) (**Table 6**)
- Using International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice criteria, SAEs resulting in hospitalization, death, a life-threatening event, or an important medical event occurred in ≤0.4% of patients across all studied treatment phases (**Table 7**)
- Respiratory depression was identified as a new event of interest; additional data collection from patient monitoring forms and analyses from the REMS program are planned

TABLE 5: Summary of AEs of interest associated with reports of SAEs

n (%)	Treatment Session		
	First session n = 58,483[a]	Sessions 1-8 n = 58,471[b]	Sessions 9-12 n = 43,908[c]
Patients with ≥1 SAE	152 (0.3)	485 (0.8)	125 (0.3)
Sedation	5 (<0.1)	12 (<0.1)	2 (<0.1)
Dissociation	15 (<0.1)	42 (0.1)	5 (<0.1)
Increased BP[d]	18 (<0.1)	71 (0.1)	14 (<0.1)

BP, blood pressure; SAE, serious adverse event.
Patient SAEs were counted once per phase; therefore, it is possible that a patient had >1 SAE within each treatment phase.
[a]n values represent patients who received at least 1 treatment in either an inpatient or outpatient treatment center.
[b]n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment session 1 and 8 (these data are inclusive of the first treatment session).
[c]n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment session 9 and 12 (inclusive).
[d]Includes blood pressure diastolic increase, BP increase, and BP systolic increase.

TABLE 6: Summary of the most common REMS-PMF SAE descriptions (≥0.1% during the first 12 treatment sessions)

n (%)	Treatment session			
	First session n = 58,483[a]	Sessions 1-8 n = 58,471[b]	Sessions 9-12 n = 43,908[c]	Sessions 1-12 n = 58,474[d]
Dissociation	15 (<0.1)	42 (0.1)	5 (<0.1)	46 (0.1)
Dizziness	19 (<0.1)	45 (0.1)	12 (<0.1)	55 (0.1)
Hypertension	15 (<0.1)	37 (0.1)	14 (<0.1)	49 (0.1)
Increased BP[e]	18 (<0.1)	71 (0.1)	14 (<0.1)	82 (0.1)
Nausea	26 (<0.1)	68 (0.1)	10 (<0.1)	77 (0.1)
Vomiting	29 (<0.1)	69 (0.1)	15 (<0.1)	82 (0.1)

ICH-GCP, International Council for Harmonisation of Technical Requirements for Pharmaceuticals; BP, blood pressure; SAE, serious adverse event.
[a]n values represent patients who received at least 1 treatment in either an inpatient or outpatient treatment center.
[b]n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment session 1 and 8 (these data are inclusive of the first treatment session).
[c]n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment session 9 and 12 (inclusive).
[d]Of these patients, 9 had first sessions that occurred at ≥13 weeks; inpatient interactions were excluded.
[e]Includes BP diastolic increase, BP increase, and BP systolic increase.

TABLE 7: SAEs by ICH-GCP criteria and treatment session

n (%)	Treatment session		
	First session n = 58,483[a]	Sessions 1-8 n = 58,471[b]	Sessions 9-12 n = 43,908[c]
Hospitalization	17 (<0.1)	70 (0.1)	30 (0.1)
Disability or permanent damage	(0)	(0)	(0)
Death	(0)	1 (<0.1)	(0)
Life threatening	1 (<0.1)	6 (<0.1)	1 (<0.1)
Important medical event[d]	74 (0.1)	237 (0.4)	62 (0.1)

ICH-GCP, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice.
[a]n values represent patients who received at least 1 treatment in either an inpatient or outpatient treatment center.
[b]n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment session 1 and 8 (data are inclusive of the first treatment session).
[c]n values represent patients who had at least 1 treatment session that was initiated in an outpatient treatment center between treatment session 9 and 12 (inclusive).
[d]Any event that jeopardized the patient or required intervention to prevent an SAE. Some events reported under this category did not strictly meet the regulatory definition but were deemed serious at the time of assessment by the reporter's subjective judgment.

Key takeaways

Actively solicited reports of sedation, dissociation, and increased blood pressure decreased over the course of ESK treatment and overall frequency of serious AEs was low

Limitations

- The REMS Patient Monitoring Form only specifically solicited AEs of sedation, dissociation, and increased BP at each treatment session
- Repeated analyses at the patient level are needed to determine how predictably AEs change over the course of ESK treatment
- These data cannot be used to predict the likelihood of an AE occurrence for any individual patient
- AE severity is not captured on the REMS Patient Monitoring Form
- Based on other post-marketing sources, respiratory depression was identified as a new adverse reaction for ESK. Further analyses are currently underway to provide additional information regarding cases of respiratory depression

Conclusions

- As anticipated, sedation and dissociation were commonly reported adverse events in the REMS program. Sedation, dissociation, and increased BP were more likely to occur during the first 8 treatment sessions compared with later sessions, and the likelihood of these events being associated with an SAE was rare
- Overall frequency of SAEs with esketamine nasal spray remains low and consistent with the safety profile described in the US prescribing information

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Disclosures

MH, BB, and PQ are employees of Janssen Scientific Affairs, LLC, a Johnson & Johnson company. IT, TD, and DK are employees of Janssen Research & Development, LLC. MH, IT, TD, BB, PQ, and DK hold stock in Johnson & Johnson. GS has served as a consultant for Allergan, Alkermes, AstraZeneca, Avanier Pharmaceuticals, Axsome Therapeutics Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol Myers Squibb, Clexio, Denovo Biopharma, Engrail Therapeutics, Gilgamesh, Hoffman-La Roche, Intra-Cellular Therapies, Janssen, Lundbeck, Merck, Naurex, Navitor Pharmaceuticals, Neurocrine, Novartis, Noven Pharmaceuticals, Otsuka, Praxis Therapeutics, Sage Pharmaceuticals, Servier Pharmaceuticals, Taisho Pharmaceuticals, Teva, Valeant, Vistagen Therapeutics, and XW Labs; has received research contracts from AstraZeneca, Bristol Myers Squibb, Eli Lilly and Company, Johnson & Johnson, Hoffman-La Roche, Merck, Naurex, Servier, and Usona; holds equity in BioHaven Pharmaceuticals; and is a co-inventor on a US patent (#8,778,979) held by Yale University and a co-inventor on US Provisional Patent Application No. 047162-7177P1 (00754) filed on August 20, 2018, by the Yale University Office of Cooperative Research. Yale University has a financial relationship with Janssen Pharmaceuticals and may receive financial benefits from this relationship. The University has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office.

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