SAFETY DATA SHEET

Version	Revision Date:	SDS Number:	Date of last issue: 2024/08/31
3.3	2024/09/04	100000014542	Date of first issue: 2018/08/20

SECTION 1. IDENTIFICATION

Substance name : SPRAVATO®
Nasal spray device Delivering 0.2 mL Solution, containing 32.3 mg of esketamine hydrochloride aqueous solution (28 mg of esketamine)

Manufacturer or supplier's details

Company name of supplier : Janssen Pharmaceuticals, Inc.

Address : 1125 Trenton-Harbourton Rd
Titusville NJ 08560

USA

Telephone : +16097302000

E-mail address of person responsible for the SDS : SDSJanssen@its.jnj.com

Emergency telephone number : **CHEMTREC US: 1-800-424-9300**
CHEMTREC International: +1 703-741-5970

Recommended use of the chemical and restrictions on use

Recommended use : Finished Pharmaceutical Product
Pharmacotherapeutic group: Psychoanaleptics
This SDS is only intended for occupational use and not for consumer use (see patient packaging insert for consumer use). This SDS is written to provide environmental, health and safety information for personnel that will be handling this finished pharmaceutical product. For health and safety information during manufacturing of this product we refer to the appropriate SDS for each component.
This dosage form is not exempt from the requirements of the OSHA Hazard Communication Standard (US OSHA Standard 29 CFR Part 1910.1200).

SECTION 2. HAZARDS IDENTIFICATION

GHS classification in accordance with the OSHA Hazard Communication Standard (29 CFR 1910.1200)

Long-term (chronic) aquatic hazard : Category 3

GHS label elements

Hazard statements : H412 Harmful to aquatic life with long lasting effects.

Precautionary statements : **Prevention:**

P273 Avoid release to the environment.

Disposal:

P501 Dispose of contents/ container to an approved waste disposal plant.

Other hazards

None known.

SECTION 3. COMPOSITION/INFORMATION ON INGREDIENTS

Substance / Mixture : Mixture

Chemical nature : Liquid

Components

Chemical name	CAS-No.	Concentration (% w/w)
(S)-(+)-ketamine hydrochloride (N*)	33643-47-9	>= 10 - < 20

Actual concentration is withheld as a trade secret

SECTION 4. FIRST AID MEASURES

If inhaled : If breathed in, move person into fresh air.
Consult a physician.

In case of skin contact : Take off contaminated clothing and shoes immediately.
Wash off with soap and water.
If symptoms persist, call a physician.

In case of eye contact : Rinse immediately with plenty of water, also under the eyelids, for at least 5 minutes.
Remove contact lenses.
If eye irritation persists, consult a specialist.

If swallowed : If swallowed, rinse mouth with water (only if the person is conscious).
Call a physician immediately.

Most important symptoms and effects, both acute and delayed : anxiety
Dissociation
Dizziness
Increased blood pressure
nausea
numbness
sedation
taste disorders
Vertigo

Vomiting
lethargy
anxiety

Notes to physician : Treat symptomatically.

SECTION 5. FIREFIGHTING MEASURES

Suitable extinguishing media : Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.

Hazardous combustion products : No information available.

Further information : No information available.

Special protective equipment for firefighters : In the event of fire, wear self-contained breathing apparatus.

SECTION 6. ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures : In the event of an accidental release the emergency response team must respond based on a risk assessment and use personal protective equipment as appropriate.
Evacuate personnel to safe areas.

Environmental precautions : Should not be released into the environment.
Do not flush into surface water or sanitary sewer system.

Methods and materials for containment and cleaning up : Large spills: Dam up. Soak up with inert absorbent material.
Keep in properly labelled containers.
Small spills: Gently cover the spill with an absorbent towel or pad.
Large spills + Small spills: Keep in suitable, closed containers for disposal. Treat recovered material as described in the section "Disposal considerations".

SECTION 7. HANDLING AND STORAGE

Advice on protection against fire and explosion : No data available

Advice on safe handling : Do not break, crush or spill this Finished Pharmaceutical Product.
To avoid thermal decomposition, do not overheat.
Use personal protective equipment as required.
Avoid inhalation, ingestion and contact with skin and eyes.

Conditions for safe storage : To maintain product quality, do not store in heat or direct sunlight.

Store in original container.
Keep containers tightly closed in a cool, well-ventilated place.
Keep away from heat and sources of ignition.

Recommended storage temperature : 59 - 77 °F / 15 - 25 °C

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Components with workplace control parameters

Components	CAS-No.	Value type (Form of exposure)	Control parameters / Permissible concentration	Basis
(S)-(+)-ketamine hydrochloride (N*)	33643-47-9	TWA	0.024 mg/m3	J&J OEL/PBOEL HHC
		STEL	0.19 mg/m3	J&J OEL/PBOEL HHC
		PBOEL-HHC	2	J&J OEL/PBOEL HHC
	Further information: J&J has a hazard banding notation: PBOEL HHC. This substance is classified by J&J as being PBOEL HHC 2.			

Engineering measures : All personal protective equipment should be based on a risk assessment. Consult a Environment Health Safety expert if necessary.
If this product is processed not in accordance with the prescribed use, contact the Industrial Hygiene / Environment Health Safety Expert to assess the situation.
Validated Industrial Hygiene Analytical methods are developed to monitor and quantify inhalable exposure to the Active Pharmaceutical Ingredient. For more information contact Bureau Veritas Laboratories - Lake Zurich (BV_LZLab@bureauveritas.com) or the Laboratory of Occupational and Environmental Hygiene (lamh.be).

Personal protective equipment

Respiratory protection : No personal respiratory protective equipment normally required.

Hand protection
Remarks : Disposable gloves

Eye protection : No special precautions required.

Skin and body protection : closed work clothing

Protective measures	:	The type of protective equipment must be selected based on the Environmental Health and Safety risk assessment. Consult a Environmental Health and Safety expert if necessary.
Hygiene measures	:	Handle in accordance with good industrial hygiene and safety practice.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance	:	solution
Colour	:	No data available
Odour	:	No data available
Odour Threshold	:	No data available
pH	:	No data available
Melting point/ range	:	No data available
Boiling point/boiling range	:	No data available
Flash point	:	No data available
Self-ignition	:	No data available
Upper explosion limit / Upper flammability limit	:	No data available
Lower explosion limit / Lower flammability limit	:	No data available
Vapour pressure	:	No data available
Relative vapour density	:	No data available
Relative density	:	No data available
Density	:	No data available

Solubility(ies)

Water solubility	:	No data available
Solubility in other solvents	:	No data available
Partition coefficient: n-octanol/water	:	No data available
Decomposition temperature	:	No data available

Viscosity

Viscosity, dynamic	:	Not applicable
Viscosity, kinematic	:	No data available

SECTION 10. STABILITY AND REACTIVITY

Reactivity	:	None reasonably foreseeable.
Chemical stability	:	Stable under normal conditions.
Possibility of hazardous reactions	:	No dangerous reaction known under conditions of normal use.
Conditions to avoid	:	To avoid thermal decomposition, do not overheat.
Incompatible materials	:	None known.
Hazardous decomposition products	:	None known.

SECTION 11. TOXICOLOGICAL INFORMATION

Acute toxicity

Product:

Acute oral toxicity : Acute toxicity estimate: 3,817 mg/kg
Method: Calculation method

Components:

(S)-(+)-ketamine hydrochloride (N*):

Acute oral toxicity : Maximum tolerated dose (Rat, male): > 160 mg/kg

Maximum tolerated dose (Rat, female): > 40 mg/kg

Assessment: The component/mixture is moderately toxic after single ingestion.

Acute inhalation toxicity : Remarks: No data available

Acute dermal toxicity : Remarks: No data available

Acute toxicity (other routes of administration) : Maximum tolerated dose (Rat): > 54 mg/kg
Application Route: intranasal (IN) administration
Method: Acute toxicity study

Skin corrosion/irritation

Components:

(S)-(+)-ketamine hydrochloride (N*):

Result : Not expected to cause skin irritation
Remarks : Information taken from reference works and the literature.

Serious eye damage/eye irritation

Components:

(S)-(+)-ketamine hydrochloride (N*):

Result : not expected to cause eye irritation
Remarks : Information taken from reference works and the literature.

Respiratory or skin sensitisation

Components:

(S)-(+)-ketamine hydrochloride (N*):

Result : Not expected to cause skin sensitization

Germ cell mutagenicity

Components:

(S)-(+)-ketamine hydrochloride (N*):

Genotoxicity in vitro : Test system: Salmonella typhimurium
Method: Ames test
Result: negative

Test system: Escherichia coli
Method: Ames test
Result: negative

Test Type: In vitro micronucleus test
Test system: human lymphoblastoid cells
Result: positive

Genotoxicity in vivo : Test Type: In vivo micronucleus test
Species: Rat
Result: negative

Test Type: comet assay
Species: Rat
Method: OECD Test Guideline 489
Result: negative

Germ cell mutagenicity - Assessment : No evidence of mutagenicity based on in vitro and in vivo studies and expert judgment.

Carcinogenicity

Components:

(S)-(+)-ketamine hydrochloride (N*):

Species	:	Rat
Application Route	:	intranasal (IN) administration
Exposure time	:	2 Years
Frequency of Treatment	:	daily
NOAEL	:	ca. 27 mg/kg
Result	:	No evidence of carcinogenicity in animal studies.

Species	:	Mouse
Application Route	:	Subcutaneous; injection made in the back or neck of animal
Exposure time	:	6 month(s)
Frequency of Treatment	:	daily
NOAEL	:	40 - 75 mg/kg
Result	:	No evidence of carcinogenicity in animal studies.

Carcinogenicity - Assessment	:	No evidence of carcinogenicity.

IARC No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

OSHA No component of this product present at levels greater than or equal to 0.1% is on OSHA's list of regulated carcinogens.

NTP No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

Reproductive toxicity

Components:

(S)-(+)-ketamine hydrochloride (N*):

Effects on fertility	:	Species: Rat, male and female Application Route: intranasal (IN) administration General Toxicity - Parent: NOAEL: ca. > 4.5 mg/kg General Toxicity F1: NOAEL: ca. > 45 mg/kg Early Embryonic Development: NOAEL: ca. > 45 mg/kg body weight GLP: yes
Effects on foetal development	:	Species: Rat, female Application Route: intranasal (IN) administration Developmental Toxicity: NOAEL: ca. > 45 mg/kg body weight Method: Developmental Toxicity Species: Rat, male and female Application Route: intranasal (IN) administration Duration of Single Treatment: 5.5 Weeks Frequency of Treatment: 2 days/week

Developmental Toxicity: NOAEL: 43.8 - 78.7 mg/kg food
Method: Developmental Toxicity

Species: Rat, male and female
Application Route: Subcutaneous
Duration of Single Treatment: 5.5 Weeks
Frequency of Treatment: 2 days/week
Developmental Toxicity: NOAEL: < 75 mg/kg food
Method: Developmental Toxicity

Reproductive toxicity - Assessment : No evidence of reprotoxicity.

Teratogenicity - Assessment : No evidence of adverse effects on development.

STOT - single exposure

Components:

(S)-(+)-ketamine hydrochloride (N*):

Target Organs : Central nervous system
Assessment : The substance or mixture is classified as specific target organ toxicant, single exposure, category 3 with narcotic effects.

STOT - repeated exposure

Components:

(S)-(+)-ketamine hydrochloride (N*):

Assessment : The substance or mixture is not classified as specific target organ toxicant, repeated exposure.

Repeated dose toxicity

Components:

(S)-(+)-ketamine hydrochloride (N*):

Species : Rat
NOAEL : ca. > 27 mg/kg
Application Route : intranasal (IN) administration
Exposure time : 6 m
Target Organs : Central nervous system

Species : Dog
NOAEL : ca. > 10 mg/kg
Application Route : intranasal (IN) administration
Exposure time : 9 m
Target Organs : Central nervous system

Aspiration toxicity

No data available

Experience with human exposure

No data available

Toxicology, Metabolism, Distribution

No data available

Neurological effects

No data available

Further information

No data available

Other health hazards

No data available

SECTION 12. ECOLOGICAL INFORMATION

Ecotoxicity

Components:

(S)-(+)-ketamine hydrochloride (N*):

Toxicity to fish	:	LC50 (Oncorhynchus mykiss (rainbow trout)): 77.5 mg/l Exposure time: 96 h Test Type: static test Method: OECD Test Guideline 203 GLP: yes
Toxicity to daphnia and other aquatic invertebrates	:	EC50 (Daphnia magna (Water flea)): 106.7 mg/l Exposure time: 48 h Test Type: Immobilization Method: OECD Test Guideline 202 GLP: yes
Toxicity to algae/aquatic plants	:	ErC50 (Pseudokirchneriella subcapitata (green algae)): 90.9 mg/l End point: Growth rate Exposure time: 72 h Test Type: Growth inhibition Method: OECD Test Guideline 201 GLP: yes
Toxicity to fish (Chronic toxicity)	:	NOEC (Brachydanio rerio (zebrafish)): 0.341 mg/l Exposure time: 30 d Test Type: Fish early-life stage (FELS) toxicity test (OECD 210) Method: OECD Test Guideline 210 GLP: yes
Toxicity to daphnia and other aquatic invertebrates (Chronic toxicity)	:	NOEC (Daphnia magna (Water flea)): 3.31 mg/l Exposure time: 21 d Test Type: Daphnia reproduction test Method: OECD Test Guideline 211

GLP: yes

Toxicity to microorganisms : NOEC (activated sludge): 100 mg/l
Exposure time: 3 h
Test Type: Respiration inhibition
Method: OECD Test Guideline 209
GLP: yes

Persistence and degradability

Components:

(S)-(+)-ketamine hydrochloride (N*):

Biodegradability : aerobic
Inoculum: activated sludge
Result: Not readily biodegradable.
Exposure time: 28 d
Method: OECD Test Guideline 301B
GLP: yes

Stability in water : Test Type: aerobic
Degradation half life (DT50): 11.4 d
Method: OECD Test Guideline 308
GLP: yes
Remarks: Fresh water 1

Test Type: aerobic
Degradation half life (DT50): 138 d
Method: OECD Test Guideline 308
GLP: yes
Remarks: total system 1

Test Type: aerobic
Degradation half life (DT50): 20.4 d
Method: OECD Test Guideline 308
GLP: yes
Remarks: Fresh water 2

Test Type: aerobic
Degradation half life (DT50): 230 d
Method: OECD Test Guideline 308
GLP: yes
Remarks: total system 2

Bioaccumulative potential

Components:

(S)-(+)-ketamine hydrochloride (N*):

Bioaccumulation : Remarks: No data available

Partition coefficient: n-octanol/water : log Pow: 2.08
pH: 9

Method: OECD Test Guideline 107
GLP: yes

Mobility in soil

Components:

(S)-(+)-ketamine hydrochloride (N*):

Distribution among environmental compartments : Adsorption/Soil
Koc: 8.79 - 466.13
Method: OECD Test Guideline 106

Other adverse effects

No data available

SECTION 13. DISPOSAL CONSIDERATIONS

Disposal methods

Waste from residues : In accordance with National, Federal, State and Local regulations.

Contaminated packaging : Empty containers should be taken to an approved waste handling site for recycling or disposal.

SECTION 14. TRANSPORT INFORMATION

International Regulations

UNRTDG
Not regulated as a dangerous good

IATA-DGR
Not regulated as a dangerous good

IMDG-Code
Not regulated as a dangerous good

Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code

Not applicable for product as supplied.

National Regulations

49 CFR
Not regulated as a dangerous good

SECTION 15. REGULATORY INFORMATION

California Prop. 65

This product does not contain any chemicals known to State of California to cause cancer, birth defects, or any other reproductive harm.

Other regulations

Restricted to professional users.

Medicinal products in the finished state, intended for the final user, are not subject to GHS labeling.

This product is not subject to TSCA and TSCA 12(b) Export notification because Food, Drugs and cosmetic products are exempt.

SECTION 16. OTHER INFORMATION

Full text of other abbreviations

J&J OEL/PBOEL HHC	:	J&J OEL/PBOEL HHC
J&J OEL/PBOEL HHC / STEL	:	Short term exposure limit
J&J OEL/PBOEL HHC / TWA	:	Time weighted average
J&J OEL/PBOEL HHC / PBOEL-HHC	:	PBOEL-HHC

AIIC - Australian Inventory of Industrial Chemicals; ASTM - American Society for the Testing of Materials; bw - Body weight; CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DOT - Department of Transportation; DSL - Domestic Substances List (Canada); ECx - Concentration associated with x% response; EHS - Extremely Hazardous Substance; ELx - Loading rate associated with x% response; EmS - Emergency Schedule; ENCS - Existing and New Chemical Substances (Japan); ErCx - Concentration associated with x% growth rate response; ERG - Emergency Response Guide; GHS - Globally Harmonized System; GLP - Good Laboratory Practice; HMIS - Hazardous Materials Identification System; IARC - International Agency for Research on Cancer; IATA - International Air Transport Association; IBC - International Code for the Construction and Equipment of Ships carrying Dangerous Chemicals in Bulk; IC50 - Half maximal inhibitory concentration; ICAO - International Civil Aviation Organization; IECSC - Inventory of Existing Chemical Substances in China; IMDG - International Maritime Dangerous Goods; IMO - International Maritime Organization; ISHL - Industrial Safety and Health Law (Japan); ISO - International Organisation for Standardization; KECI - Korea Existing Chemicals Inventory; LC50 - Lethal Concentration to 50 % of a test population; LD50 - Lethal Dose to 50% of a test population (Median Lethal Dose); MARPOL - International Convention for the Prevention of Pollution from Ships; MSHA - Mine Safety and Health Administration; n.o.s. - Not Otherwise Specified; NFPA - National Fire Protection Association; NO(A)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; NOELR - No Observable Effect Loading Rate; NTP - National Toxicology Program; NZIoC - New Zealand Inventory of Chemicals; OECD - Organization for Economic Co-operation and Development; OPPTS - Office of Chemical Safety and Pollution Prevention; PBT - Persistent, Bioaccumulative and Toxic substance; PICCS - Philippines Inventory of Chemicals and Chemical Substances; (Q)SAR - (Quantitative) Structure

Activity Relationship; RCRA - Resource Conservation and Recovery Act; REACH - Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals; RQ - Reportable Quantity; SADT - Self-Accelerating Decomposition Temperature; SARA - Superfund Amendments and Reauthorization Act; SDS - Safety Data Sheet; TCSI - Taiwan Chemical Substance Inventory; TECI - Thailand Existing Chemicals Inventory; TSCA - Toxic Substances Control Act (United States); UN - United Nations; UNRTDG - United Nations Recommendations on the Transport of Dangerous Goods; vPvB - Very Persistent and Very Bioaccumulative

This SDS received a major version update triggered by a periodical review of the totality of the content.

Revision Date : 2024/09/04

Date and Number Formats

This document uses the following notation for printing dates and numbers:

Date:	Dec 31th, 2012	as	2012/12/31
Numbers:	123456,78	as	123,456.78

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