SAFETY DATA SHEET

SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/ UNDERTAKING

Contact information

General

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Product identifier

Neostigmine Methylsulfate Injection

Synonyms

(*m*-hydroxyphenyl) trimethylammonium methylsulfate dimethylcarbamate.

Trade names

Not applicable

Chemical family

Mixture

Relevant identified uses of the substance or mixture and uses advised against

Bulk formulated pharmaceutical mixture/Formulated pharmaceutical product/ mixture packaged in final form for patient use

Note

This SDS is written to address potential worker health and safety issues associated with the handling of the formulated product. Workers manufacturing this product should consult the SDSs of each hazardous ingredient for hazard information and handling recommendations.

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture

Drugs in the finished state and intended for the final user are not subject to labeling in the US, EU or Canada. Please consult the prescribing/packaging information. **The classification and labeling listed below is for bulk drug product.**

SECTION 2 - HAZARDS IDENTIFICATION …continued

Globally Harmonized System [GHS] Acute toxicity - oral - Category 4.

Label elements

GHS hazard pictogram

GHS signal word Warning

GHS hazard statements H302 - Harmful if swallowed.

GHS precautionary statements P264 - Wash hands thoroughly after handling. P270 - Do not eat, drink or smoke when using this product. P301+P312: IF SWALLOWED: Call a Poison Center or doctor/physician if you feel unwell. P330 - Rinse mouth. P501 - Dispose of contents/container to location in accordance with local/regional/national/ international regulations.

Other hazards Neostigmine methylsulfate is a cholinesterase inhibitor indicated for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery. It may also be used to treat myasthenia gravis. It is usually give subcutaneously or intramuscularly, at a dose of 0.25 to 0.5 mg. Side effects may include salivation and excess bronchial secretions and runny nose, muscle tremors, bowel cramps and diarrhea, heartbeat irregularities, and increased urination. Overdosage may lead to increasing muscle weakness and respiratory arrest due to cholinergic crisis.

Note This mixture is classified as hazardous according to Regulation EC No 1272/2008 (EU CLP) and Hazard Communication Standard No. 1910.1200 (US OSHA). The pharmacological, toxicological and ecological properties of this mixture have not been fully characterized. See Section 16 for full GHS classifications.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	GHS Classification
Neostigmine Methylsulfate	51-60-5	200-109-5	≤0.1%	ATO2: H300
Phenol	108-95-2	203-632-7	<0.5%	SC1B: H314; ATI3: H331; ATD3: H311; ATO3: H301; STOT-R2: H373; GCM2: H341

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS …continued

Note	The ingredient(s) listed above are considered dangerous/hazardous and/or are pharmacologically active. The remaining components of the drug solution are non-hazardous or present below reportable limits. See Section 16 for full text of GHS classifications.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures

Immediate Medical Attention Needed	Yes
Eye Contact	If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.
Skin Contact	Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.
Inhalation	Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.
Ingestion	Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.
Protection of first aid responders	See Section 8 for Exposure Controls/Personal Protection recommendations.
Most important symptoms and effects, both acute and delayed	See Sections 2 and 11.
Indication of immediate medical attention and special treatment needed, if necessary	Medical conditions aggravated by exposure: None known or reported. Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective package or prescribing information for potential drug interactions.

SECTION 5 - FIREFIGHTING MEASURES

Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Specific hazards arising from the substance or mixture	No information identified. May emit carbon monoxide and carbon dioxide, oxides of nitrogen, and sulfur-containing compounds.

SECTION 5 - FIREFIGHTING MEASURES …continued

Flammability/ Explosivity	As product is an aqueous solution, it is not expected to be flammable or explosive.
Advice for firefighters	Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe mist/vapors/spray.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	DO NOT CAUSE MATERIAL TO BECOME AIRBORNE. For small spills, soak up material with absorbent, e.g., paper towels. For large spills, cordon off spill area and minimize the spreading of spilled material. Soak up material with absorbent. Collect spilled material, absorbent, and rinse water into suitable containers for proper disposal in accordance with applicable waste disposal regulations (see Section 13). Decontaminate the area twice with an appropriate solvent (see Section 9).
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	Follow recommendations for handling potent pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing vapor/mist/spray. Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store at 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.) Protect from light. Store in carton until time of use.
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note	Dispose of broken vials in a sharps container.

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Phenol	ACGIH	TLV-TWA	5 ppm (skin)
	OSHA	PEL	5 ppm (skin)
	NIOSH	REL - TWA	20 mg/m3
	NIOSH	REL-Ceiling	60 mg/m^3

Exposure/Engineering controls

None required for normal handling of packaged product. If handling bulk product or vials are opened/crushed/broken: Control exposures to below the OEL (if available). Otherwise, selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Open handling should not be performed when handling potent substances, or substances of unknown toxicity. Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for dusts and/or aerosols.

Respiratory protection

None required for normal handling of packaged product. If handling bulk product or vials are opened/crushed/broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine powder handling tasks, an approved and properly worn powered air-purifying respirator equipped with HEPA filters or combination filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a positive-pressure air-supplied respirator if there is any potential for an uncontrolled release, when exposure levels are not known, or in any other circumstances where air purifying respirators may not provide adequate protection.

Hand protection

None required for normal handling of packaged product. Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered.

Skin protection

Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.

Eye/face protection

Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.

Environmental Exposure Controls

Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.

Other protective measures

Wash hands in the event of contact with this substance, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Solution
Color	Clear, colorless
Odor	Odorless
Odor threshold	No information identified.
pH	5.4 to 5.6
Melting point/ freezing point	No information identified.
Initial boiling point and boiling range	No information identified.
Flash point	No information identified.
Evaporation rate	No information identified.
Flammability (solid, gas)	Not applicable.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	No information identified.
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	Very soluble.
Solvent solubility	Soluble in alcohol
Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Other information

Molecular weight Not applicable (Mixture)

Molecular formula Not applicable (Mixture)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity No information identified.

Chemical stability Stable under normal handling and storage conditions.

Possibility of hazardous reactions Not expected to occur.

Conditions to avoid No information identified.

Incompatible materials No information identified.

Hazardous decomposition products No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note No data for this product/mixture were identified. The following data describe the active ingredient and/or the individual ingredients where applicable.

Information on toxicological effects

Route of entry May be absorbed by inhalation, skin contact, eye contact, and ingestion.

Acute toxicity

Compound	Type	Route	Species	Dose
Neostigmine Methylsulfate	LD_{50}	Oral	Mice	7.5 mg/kg
	LD_{50}	Intravenous (IV)	Mice	0.16 mg/kg
	LD_{50}	Subcutaneous (SC)	Rat	0.33 mg/kg
Phenol	LD_{50}	Oral	Rodents	300-600 mg/kg
	LD_{50}	Dermal	Rat/Rabbit	670-1400 mg/kg
	LC_{50} (8 hour)	Inhalation	Rat	>900 mg/m^3

Irritation/Corrosion Phenol can be corrosive to the skin.

Sensitization No studies identified.

STOT-single exposure Clinical signs in acute toxicity studies of neostigmine were consistent with muscarinic effects, including skeletal muscle weakness and twitching, constricted pupils, excessive salivation, intestinal hypermotility, difficulty breathing, and slowed heart rate.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

STOT-repeated exposure/Repeat-dose toxicity	Tolerance appears to develop after repeated dosing of neostigmine. Rats were given 0.1 mg SC neostigmine twice daily for 22 to 25 days. Initial signs included tremors, ruffled fur, excess salivation, rapid breathing, weakness, and decreased activity. Severity declined after 4 to 6 days of dosing and were largely absent after 4 weeks. Repeated exposure to phenol by inhalation caused lung damage in rats.
Reproductive toxicity	No reproductive effects were noted in a rat reproductive study of neostigmine at IV doses of up to 8.1 µg/kg/day.
Developmental toxicity	NOAELs in a standard battery of developmental toxicity studies were the highest IV doses tested of 50 and 40 µg/kg/day neostigmine in rats and rabbits, respectively. This dose was associated with maternal effects (muscle twitching).
Genotoxicity	Neostigmine methylsulfate was nonmutagenic in the Ames assay. It was not clastogenic *in vitro* (chromosomal aberration assay in peripheral blood lymphocytes) or *in vivo* (mouse micronucleus test). Phenol is not mutagenic in the Ames assay but was mutagenic and clastogenic in mammalian cells. Results from an *in vivo* mouse micronucleus test were inconsistent, with some positive reports at high doses.
Carcinogenicity	Phenol is listed as Group 3: Not classifiable as to its carcinogenicity to humans, by IARC. None of the other components of the mixture present at levels greater than or equal to 0.1% are listed by NTP, IARC, ACGIH or OSHA as a carcinogen.
Aspiration hazard	No studies identified
Human health data	See "Section 2 - Other Hazards"

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Neostigmine Methylsulfate	--	--	--
Phenol	--	--	--

Persistence and Degradability	No data identified.
Bioaccumulative potential	No data identified.
Mobility in soil	No data identified.
Results of PBT and vPvB assessment	Not performed.
Other adverse effects	No data identified.
Note	The environmental characteristics of this product have not been fully investigated. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods	Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

Transport	Based on the available data, this product is not regulated as a hazardous material/ dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.
UN number	None assigned.
UN proper shipping name	None assigned.
Transport hazard classes and packing group	None assigned.
Environmental hazards	Based on the available data, this product/mixture is not regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Avoid release to the environment.
Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	Not applicable.

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS generally complies with the requirements listed under current guidelines in the US, EU and Canada. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed.
California proposition 65	Not listed.
Additional information	No other information identified.

SECTION 16 - OTHER INFORMATION

Full text of H phrases and GHS classifications	ATO2 - Acute Toxicity (Oral) Category 2. H300 - Fatal if swallowed. ATI3 - Acute Toxicity (Inhalation) Category 3. H331 - Toxic if inhaled. ATD3 - Acute Toxicity (Dermal) Category 3. H311 - Toxic in contact with skin. ATO3 - Acute Toxicity (Oral) Category 3. H301 - Toxic if swallowed. ATO4 - Acute Toxicity (Oral) Category 4. H302 - Harmful if swallowed. STOT-R2 - Specific Target Organ Toxicity Following Repeated Exposure Category 2. H373 - May cause damage to the lungs through prolonged or repeated exposure. GCM2 - Germ Cell Mutagenicity Category 2. H341 - Suspected of causing genetic defects.
Sources of data	Information from published literature and internal company data.
Abbreviations	ACGIH - American Conference of Governmental Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; CLP - Classification, Labelling, and Packaging of Substances and Mixtures; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STOT - Specific Target Organ Toxicity; STEL - Short Term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System
Issue Date	9 May 2016
Revisions	This is the first version of this SDS.
Disclaimer	The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions. No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a potent pharmaceutical

Disclaimer …continued

product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.