SAFETY DATA SHEET

Product Name: Midazolam Injection, USP

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Manufacturer Name And Address	Hospira, Inc. 275 North Field Drive Lake Forest, Illinois 60045 USA
Emergency Telephone	CHEMTREC: North America: 800-424-9300; International 1-703-527-3887; Australia - 61-290372994; UK - 44-870-8200418
Hospira, Inc., Non-Emergency	224 212-2000
Product Name	Midazolam Injection, USP
Synonyms	8-Chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo(1,5-a)(1,4)benzodiazepine hydrochloride

2. HAZARD(S) IDENTIFICATION

Emergency Overview

Midazolam Injection, USP is a solution containing midazolam hydrochloride, a short-acting benzodiazepine central nervous system depressant used to relieve anxiety and provide sedation. In the U.S., midazolam is subject to Schedule IV control under the Controlled Substances Act. In the workplace, midazolam hydrochloride should be considered a potent drug and a potential occupational reproductive hazard. Based on clinical use, possible target organs include the nervous system, gastrointestinal system, genitourinary system, and cardiovascular system.

U.S. OSHA GHS Classification

Physical Hazards	**Hazard Class**	**Hazard Category**
	Not Classified	Not Classified
Health Hazards	**Hazard Class**	**Hazard Category**
	Toxic to Reproduction	2

Label Element(s)

Pictogram

Signal Word

Warning

Hazard Statement(s)

Suspected of damaging fertility or the unborn child

Precautionary Statement(s)

Prevention

Obtain special instructions before use
Do not handle until all safety precautions have been read and understood
Wear protective gloves/protective clothing/eye protection/face protection
Do not breathe vapor or spray
Wash hands thoroughly after handling

Response

If exposed or concerned: Get medical advice/attention. Get medical attention if you feel unwell.

IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists, get medical attention.

3. COMPOSITION/INFORMATION ON INGREDIENTS

Active Ingredient Name Midazolam Hydrochloride
Chemical Formula $C_{18}H_{13}ClFN_3$•HCl

Component	Approximate Percent by Weight	CAS Number	RTECS Number
Midazolam Hydrochloride	≤ 0.5	59467-96-8	NI2922250

Non-hazardous ingredients include Water for Injection. Hazardous ingredients present at less than 1% include sodium chloride; hydrochloric acid and/or sodium hydroxide are used to adjust the pH.

4. FIRST AID MEASURES

Eye Contact Remove from source of exposure. Flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

Skin Contact Remove from source of exposure. Flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

Inhalation Remove from source of exposure. If signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

Ingestion Remove from source of exposure. If signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary. Treatment of injectable midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation, including administration of oxygen. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of midazolam overdosage. Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. There are anecdotal reports of reversal of adverse hemodynamic responses associated with midazolam hydrochloride following administration of flumazenil to pediatric patients. Prior to the administration of flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. Flumazenil will only reverse benzodiazepine-induced effects but will not reverse the effects of other concomitant medications. The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in longterm benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, should be consulted prior to use.

5. FIRE FIGHTING MEASURES

Flammability None anticipated from this aqueous product.

Fire & Explosion Hazard None required from this aqueous product.

Extinguishing Media As with any fire, use extinguishing media appropriate for primary cause of fire such as carbon dioxide, dry chemical extinguishing powder or foam.

Special Fire Fighting Procedures No special provisions required beyond normal firefighting equipment such as flame and chemical resistant clothing and self contained breathing apparatus.

6. ACCIDENTAL RELEASE MEASURES

Spill Cleanup and Disposal Isolate area around spill. Put on suitable protective clothing and equipment as specified by site spill control procedures. Absorb the liquid with suitable material and clean affected area with soap and water. Dispose of spill materials according to the applicable federal, state, or local regulations.

7. HANDLING AND STORAGE

Handling No special handling required for hazard control under conditions of normal product use. However, in the U.S., midazolam is subject to Schedule IV control under the Controlled Substances Act.

Storage No special storage required for hazard control. For product protection, follow storage recommendations noted on the product case label, the primary container label, or the product insert.

Special Precautions No special precautions required for hazard control.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Exposure Guidelines

	Exposure Limits			
Component	**OSHA-PEL**	**ACGIH-TLV**	**AIHA WEEL**	**Hospira EEL**
Midazolam Hydrochloride	8-hr TWA: Not Established	8-hr TWA: Not Established	8-hr TWA: Not Established	8-hr TWA: Not Established

Notes: OSHA PEL: US Occupational Safety and Health Administration – Permissible Exposure Limit
ACGIH TLV: American Conference of Governmental Industrial Hygienists – Threshold Limit Value.
AIHA WEEL: Workplace Environmental Exposure Level
EEL: Employee Exposure Limit.
TWA: 8-hour Time Weighted Average.

Respiratory Protection Respiratory protection is normally not needed during intended product use. However, if the generation of aerosols is likely, and engineering controls are not considered adequate to control potential airborne exposures, the use of an approved air-purifying respirator with a HEPA cartridge (N95 or equivalent) is recommended under conditions where airborne aerosol concentrations are not expected to be excessive. For uncontrolled release events, or if exposure levels are not known, provide respirators that offer a high protection factor such as a powered air purifying respirator or supplied air. A respiratory protection program that meets OSHA's 29 CFR 1910.134 and ANSI Z88.2 requirements must be followed whenever workplace conditions require respirator use. Personnel who wear respirators should be fit tested and approved for respirator use as required.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION: continued

Skin Protection	If skin contact with the product formulation is likely, the use of latex or nitrile gloves is recommended.
Eye Protection	Eye protection is normally not required during intended product use. However, if eye contact is likely to occur, the use of chemical safety goggles (as a minimum) is recommended.
Engineering Controls	Engineering controls are normally not needed during the anticipated use of this product.

9. PHYSICAL/CHEMICAL PROPERTIES

Appearance/Physical State	A sterile, non-pyrogenic solution
Odor	NA
Odor Threshold	NA
pH	3 (2.5 to 3.5)
Melting point/Freezing Point	NA
Initial Boiling Point/Boiling Point Range	NA
Flash Point	NA
Evaporation Rate	NA
Flammability (solid, gas)	NA
Upper/Lower Flammability or Explosive Limits	NA
Vapor Pressure	NA
Vapor Density (Air =1)	NA
Relative Density	NA
Solubility	The hydrochloride salt of midazolam, which is formed in situ, is soluble in aqueous solutions.
Partition Coefficient: n-octanol/water	NA
Auto-ignition Temperature	NA
Decomposition Temperature	NA
Viscosity	NA

10. STABILITY AND REACTIVITY

Reactivity	Not determined.
Chemical Stability	Stable under standard use and storage conditions.
Hazardous Reactions	Not determined
Conditions to Avoid	Not determined
Incompatibilities	Not determined
Hazardous Decomposition Products	Not determined. During thermal decomposition, it may be possible to generate irritating vapors and/or toxic fumes of carbon oxides (COx), nitrogen oxides (NOx), hydrogen chloride, and/or hydrogen fluoride.
Hazardous Polymerization	Not anticipated to occur with this product.

11. TOXICOLOGICAL INFORMATION

Acute Toxicity - Not determined for the product formulation. Information for active ingredient is as follows:

Ingredient(s)	Percent	Test Type	Route of Administration	Value	Units	Species
Midazolam	100	LD50	Oral	215	mg/kg	Rat
Midazolam	100	LD50	Intravenous	75, 357	mg/kg	Rat
Midazolam	100	LD50	Intravenous	50	mg/kg	Mouse
Midazolam	100	LD50	Intramuscular	> 50	mg/kg	Rat, Mouse

LD 50: Dosage that produces 50% mortality.

Occupational Exposure Potential

Information on the absorption of this product via inhalation or skin contact is not available. Published reports have indicated that some benzodiazepines have the potential to be absorbed through intact skin or mucus membranes. Avoid liquid aerosol generation and skin contact.

Signs and Symptoms

None anticipated from normal handling of this product. This product should be considered potentially irritating to the eyes and respiratory tract. In clinical use, common adverse effects include drowsiness, sedation, muscle weakness, and ataxia. Less frequent adverse effects include vertigo, headache, confusion, depression, slurred speech, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disturbances, decreased blood pressure, changes in salivation, and amnesia. Death due to respiratory depression, hypotension, or cardiac arrest has been reported infrequently in patients given intravenous midazolam for conscious sedation.

Aspiration Hazard

None anticipated from normal handling of this product.

Dermal Irritation/Corrosion

None anticipated from normal handling of this product.

Ocular Irritation/Corrosion

None anticipated from normal handling of this product. However, inadvertent contact of this product with eyes may produce redness and discomfort

Dermal or Respiratory Sensitization

None anticipated from normal handling of this product. In clinical use, allergic reactions including anaphylactoid reactions, hives, rash, pruritus have been reported infrequently.

Reproductive Effects

None anticipated from normal handling of this product. A reproduction study in male and female rats did not show any impairment of fertility at dosages up to 10 times the human intravenous dose of 0.35 mg/kg. Teratology studies conducted with midazolam maleate injectable in rabbits and rats at doses that were 5 and 10 times the human dose of 0.35 mg/kg did not show evidence of teratogenicity. Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested were approximately 10 times the human dose of 0.35 mg/kg.

Mutagenicity

Midazolam was not mutagenic in Salmonella typhimurium (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes or in the micronucleus test in mice.

Carcinogenicity

Midazolam maleate was administered with diet in mice and rats for 2 years at dosages of 1, 9 and 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high-dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (25 times a human dose of 0.35 mg/kg) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

11. TOXICOLOGICAL INFORMATION: continued

Carcinogen Lists	**IARC:** Not listed	**NTP:** Not listed	**OSHA:** Not listed

Specific Target Organ Toxicity – Single Exposure	NA
Specific Target Organ Toxicity – Repeat Exposure	Based on clinical use, possible target organs include the nervous system, gastrointestinal system, genitourinary system, and cardiovascular system.

12. ECOLOGICAL INFORMATION

***Aquatic Toxicity**	Not determined for the product. Information for ingredients is as follows: LC50(48hr) = 7.1 mg/l in Daphnia LC50 = 4.3 mg/l in rainbow trout EbC50(72hr) = 11.4 mg/l in algae (the no-observable biological effect concentration on growth (72hr) was 3.7 mg/l).
***Persistence/Biodegradability**	Not determined for the product. Information for ingredients is as follows: Midazolam was only 6% biodegraded in 28 days in the Sturm test. The EC50 (3h) for inhibition of microbial respiration was greater than 100 mg/l indicating that this material was non- inhibitory to microorganisms in the activated sludge respiration inhibition test.
Bioaccumulation	Not determined for the product.
Mobility in Soil	Not determined for the product.

* Hoffman-La Roche MSDS

Notes:

1. LC50: Concentration in water that produces 50% mortality in fish or Daphnia.
2. EC50: Concentration in water that produces 50% inhibition of growth in algae or immobilization in Daphnia.

13. DISPOSAL CONSIDERATIONS

Waste Disposal	All waste materials must be properly characterized. Further, disposal should be performed in accordance with the federal, state or local regulatory requirements.
Container Handling and Disposal	Dispose of container and unused contents in accordance with federal, state and local regulations.

14. TRANSPORTATION INFORMATION

ADR/ADG/ DOT STATUS	Not regulated
Proper Shipping Name	NA
Hazard Class	NA
UN Number	NA
Packing Group	NA
Reportable Quantity	NA
ICAO/IATA STATUS	Not regulated
Proper Shipping Name	NA
Hazard Class	NA
UN Number	NA
Packing Group	NA
Reportable Quantity	NA
IMDG STATUS	Not regulated
Proper Shipping Name	NA
Hazard Class	NA
UN Number	NA
Packing Group	NA
Reportable Quantity	NA

Notes: DOT - US Department of Transportation Regulations

15. REGULATORY INFORMATION

US TSCA Status	Exempt
US CERCLA Status	Not listed
US SARA 302 Status	Not listed
US SARA 313 Status	Not listed
US RCRA Status	Not listed
US PROP 65 (Calif.)	Not listed

Notes: TSCA, Toxic Substance Control Act; CERCLA, US EPA law, Comprehensive Environmental Response, Compensation, and Liability Act; SARA, Superfund Amendments and Reauthorization Act; RCRA, US EPA, Resource Conservation and Recovery Act; Prop 65, California Proposition 65

GHS/CLP Classification*

*In the EU, classification under GHS/CLP does not apply to certain substances and mixtures, such as medicinal products as defined in Directive 2001/83/EC, which are in the finished state, intended for the final user.

Hazard Class	Hazard Category	Pictogram	Signal Word	Hazard Statement
NA	NA	NA	NA	NA

Prevention

Obtain special instructions before use
Do not handle until all safety precautions have been read and understood
Wear protective gloves/protective clothing/eye protection/face protection
Do not breathe vapor or spray
Wash hands thoroughly after handling

Response

If exposed or concerned: Get medical advice/attention. Get medical attention if you feel unwell.

IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists, get medical attention.

15. REGULATORY INFORMATION: continued

EU Classification*	*Medicinal products are exempt from the requirements of the EU Dangerous Preparations Directive.
Classification(s)	NA
Symbol	NA
Indication of Danger	NA
Risk Phrases	NA
Safety Phrases	S23: Do not breathe vapor/spray S24: Avoid contact with the skin S25: Avoid contact with eyes S37/39 Wear suitable gloves and eye/face protection.

16. OTHER INFORMATION

Notes:

ACGIH TLV	American Conference of Governmental Industrial Hygienists – Threshold Limit Value
CAS	Chemical Abstracts Service Number
CERCLA	US EPA law, Comprehensive Environmental Response, Compensation, and Liability Act
DOT	US Department of Transportation Regulations
EEL	Employee Exposure Limit
IATA	International Air Transport Association
LD_{50}	Dosage producing 50% mortality
NA	Not applicable/Not available
NE	Not established
NIOSH	National Institute for Occupational Safety and Health
OSHA PEL	US Occupational Safety and Health Administration – Permissible Exposure Limit
Prop 65	California Proposition 65
RCRA	US EPA, Resource Conservation and Recovery Act
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
STEL	15-minute Short Term Exposure Limit
STOT - SE	Specific Target Organ Toxicity – Single Exposure
STOT - RE	Specific Target Organ Toxicity – Repeated Exposure
TSCA	Toxic Substance Control Act
TWA	8-hour Time Weighted Average

MSDS Coordinator: Hospira GEHS
Date Prepared: October 19, 2012
Date Revised: June 02, 2014

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