MATERIAL SAFETY DATA SHEET

Product Name: Midazolam Hydrochloride Injection, Solution

1. CHEMICAL PRODUCT AND COMPANY INFORMATION

Manufacturer Name And Address	Hospira Inc. 275 North Field Drive Lake Forest, Illinois USA 60045
Emergency Telephone	CHEMTREC: North America: 800-424-9300; International 1-703-527-3887; Australia (02) 8014 4880
Hospira, Inc., Non-Emergency	224-212-2000
Product Name	Midazolam Hydrochloride Injection, Solution
Synonyms	8-Chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo(1,5-a)(1,4)benzodiazepine hydrochloride

2. COMPOSITION/INFORMATION ON INGREDIENTS

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

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

3. HAZARD INFORMATION

Carcinogen List

Substance	IARC	NTP	OSHA
Midazolam Hydrochloride	Not Listed	Not Listed	Not Listed

Emergency Overview	Midazolam Hydrochloride Injection, Solution contains 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. Possible target organs include the central nervous system, gastrointestinal system, genitourinary system, cardiovascular system, and possibly the fetus.
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	During occupational use, 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.
Medical Conditions Aggravated by Exposure	Pre-existing hypersensitivity to midazolam hydrochloride, related benzodiazepines, or other ingredients in this product. Pre-existing central nervous system, gastrointestinal system, genitourinary system, and cardiovascular system ailments; pregnancy.

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 Carbon Dioxide, Foam, As with any fire, use extinguishing media appropriate for primary cause of fire.

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 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	**Type**	**mg/m3**	**ppm**	**µg/m3**	**Note**
Midazolam Hydrochloride	Hospira EEL	N/A	N/A	2	

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 (N99 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.

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	Liquid
Color	Midazolam is a white to light yellow crystalline compound, insoluble in water. Midazolam Injection is a solution.
Odor	NA
Odor Threshold:	NA
pH:	3 (2.5 to 3.5)
Melting point/Freezing point:	NA
Initial Boiling Point/Boiling Point Range:	Not Determined
Evaporation Rate:	NA
Flammability (solid, gas):	NA
Upper/Lower Flammability or Explosive Limits:	NA
Vapor Pressure:	Not Determined
Vapor Density:	Not Determined
Specific Gravity:	Not Determined
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

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 ingredients 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

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. Midazolam produced minimal eye irritation in a study in animals. 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 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.

Target Organ Effects Based on clinical use, possible target organs include the central nervous system, gastrointestinal system, genitourinary system, cardiovascular system, and possibly the fetus.

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 product.
Mobility in Soil	Not determined for the product.

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

DOT STATUS	Not regulated
ICAO/IATA STATUS:	Not regulated
IMDG STATUS:	Not regulated

15. REGULATORY INFORMATION

USA Regulations

Substance	TSCA Status	CERCLA Status	SARA 302 Status	SARA 313 Status	PROP 65 Status
Midazolam Hydrochloride	Not Listed	Not Listed	Not Listed	Not Listed	Listed

US RCRA Status	Not Listed
U.S. OSHA Classification	Target Organ Toxin Reproductive Toxin
GHS 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	Not Applicable
Hazard Category	Not Applicable
Signal Word	Not Applicable
Symbol	Not Applicable

Prevention	P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. P280.2 - Wear protective gloves and eye/face protection. P281 - Use personal protective equipment as required.
Hazard Statement	Not Applicable
Response:	If exposed or concerned: Get medical attention. 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. Wash hands after handling.

EU Classification*

*Medicinal products are exempt from the requirements of the EU Dangerous Preparations Directive. Information provided below is for the pure drug substance Midazolam Hydrochloride

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Classification(s):	Not Applicable
Symbol:	Not Applicable
Indication of Danger:	Not Applicable
Risk Phrases:	Not Applicable
Safety Phrases:	S23 - Do not breathe vapor. S24 - Avoid contact with 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
LD50	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
TSCA	Toxic Substance Control Act
TWA	8-hour Time Weighted Average

MSDS Coordinator: Hospira GEHS
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