SAFETY DATA SHEET

1. Identification

Product Identifier: Midazolam Injection, USP CIV

Synonyms: 4H-Imidazo[1,5-a][1,4]benzodiazepine, 8-chloro-6-(2-fluorophenyl)-1-methyl-,

National Drug Code (NDC):
17478-522-02
17478-522-20
17478-523-02
17478-523-05
17478-523-10
17478-523-25
17478-523-55
17478-524-01
17478-524-02
17478-524-05
17478-524-10
17478-524-15

Recommended Use: Pharmaceutical.

Company:
Akorn, Inc.
1925 West Field Court, Suite 300
Lake Forest, Illinois 60045

Contact Telephone: 1-800-932-5676

E mail: customer.service@akorn.com

Emergency Phone Number: CHEMTREC 1-800-424-9300 (U.S. and Canada)

2. Hazard(s) Identification

Physical Hazards: Not classifiable.

Health Hazards: Toxic to reproduction Category 2

Symbol(s):

Signal Word: Warning.

Hazard Statement(s):
H361 Suspected of damaging fertility or the unborn child.

Precautionary Statement(s):
P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.

P280	Wear protective gloves/protective clothing/eye protection/ face protection
P260	Do not breathe dust/fume/gas/vapor/spray.
P264	Wash hands thoroughly after handling.
P308 + P313	If exposed or concerned: Get medical advice/attention.
P314	Get medical attention if you feel unwell.
P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contacts lenses, if present and easy to do. Continue rinsing.
P337 + P313	If eye irritating persists: Get medical advice/attention.

Hazards Not Otherwise Classified: Not classifiable.

Supplementary Information: None.

3. Composition/Information on Ingredients

Chemical Name	CAS Number	Synonyms	Chemical Formula	Molecular Weight	Percentage
Midazolam Hydrochloride	59467-96-8	4H-Imidazo[1,5-a][1,4]benzodiazepine, 8-chloro-6-(2-fluorophenyl)-1-methyl-,	$C_{18}H_{13}ClFN_3$•HCl	362.25	0.1% or 0.5%

*The formula also contains Sodium Chloride, 0.8%; Disodium Edetate, 0.01%; Benzyl Alcohol, 1%; The pH is adjusted to 3.3 – 3.5 with Sodium Hydroxide and/or Hydrochloric.

4. First Aid Measures

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.
Eye Contact:	Remove from source of exposure. Flush with copious amounts of water for at least 15 minutes. If irritation persists or signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary. Ensure that medical personnel are aware of the material(s) involved and are aware of precautions to protect themselves.
Skin Contact:	Remove from source of exposure. Remove and isolate contaminated clothing and shoes. Flush with copious amounts of water for at least 20 minutes. Use soap. If irritation persists or signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary. Ensure that medical personnel are aware of the material(s) involved and are aware of precautions to protect themselves.
Inhalation:	Remove from source of exposure. Move individual(s) to fresh air. Give artificial respiration if individual(s) are not breathing and call emergency medical service. If signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary. Ensure that

	medical personnel are aware of the material(s) involved and are aware of precautions to protect themselves.
Protection of First-Aiders:	Use personal protective equipment (see section 8).
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, cardiovascular system, eye, or skin ailments; pregnancy.
Notes to Physician:	Treat supportively and symptomatically.

5. Firefighting Measures

Flammability:	None anticipated from this aqueous product.
Suitable Extinguishing Media:	Carbon dioxide, dry chemical, foam. As with any fire, use extinguishing media appropriate for primary cause of fire.
Unsuitable Extinguishing Media:	Not determined.
Special Fire Fighting Procedures:	No special provisions required beyond normal firefighting equipment such as flame and chemical resistant clothing and self-contained breathing apparatus.

Specific Hazards Arising from the Chemical:

Hazardous Combustion Products:	Not determined.
Other Specific Hazards:	Not determined.
Special Protective Equipment/ Precautions for Firefighters:	Wear self-contained breathing apparatus and full and protective gear.

6. Accidental Release Measures

Personal Precautions:	Use personal protective equipment recommended in Section 8 of this document and isolate the hazard area.
Personal Protective Equipment:	For personal protection see section 8.

Methods for Cleaning Up: 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.

Environmental Precautions: No data available.

Reference to Other Sections: Refer to Sections 8, 12 and 13 for further information.

7. Handling and Storage

Precautions for Safe Handling: Handle in accordance with product label and/or product insert information. However, in the U.S., midazolam is subject to Schedule IV control under the Controlled Substances Act. Handle in accordance with good industrial hygiene and safety practices.

Conditions for Safe Storage, Including Any Incompatibilities: 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.

Specific End Use: Pharmaceuticals.

8. Exposure Controls/Personal Protection

Occupational Exposure Guidelines:

Common or Chemical Name	Employee Exposure Limits
Midazolam Hydrochloride	Not established.
Benzyl Alcohol	AIHA WEEL: 10 ppm, 8-hr TWA

Engineering Controls: Engineering controls are normally not needed during the anticipated use of this product.

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.

Eyes Protection:	Not required for the normal use of this product. Safety glasses with side shields are recommended. Face shields or goggles may be required if splash potential exists or if corrosive materials are present. Approved eye protection (e.g., bearing the ANSI Z87 or CSA stamp) is preferred. Maintain eyewash facilities in the work area.
Hand Protection:	Not required for the normal use of this product. Chemically compatible gloves. For handling solutions, ensure that the glove material is protective against the solvent being used. Use handling practices that minimize direct hand contact. Employees who are sensitive to natural rubber (latex) should use nitrile or other synthetic non-latex gloves. Use of powdered latex gloves should be avoided due to the risk of latex allergy.
Skin Protection:	Not required for the normal use of this product. Wear protective laboratory coat, apron, or disposable garment when working with large quantities.

9. Physical and Chemical Properties

Physical State/Color:	A sterile, non-pyrogenic solution.
Odor:	No data available.
Odor Threshold:	No data available.
pH:	3 (2.5 – 3.5).
Melting Point:	No data available.
Freezing Point:	No data available.
Boiling Point:	No data available.
Flash Point:	No data available.
Evaporation Rate:	No data available.
Flammability (solid, gas):	No data available.
Flammability Limit - Lower:	No data available.
Flammability Limit - Upper:	No data available.
Vapor Pressure:	No data available.
Vapor Density:	No data available.
Relative Density:	No data available.
Solubility(ies):	The hydrochloride salt of midazolam, which is formed in situ, is soluble in aqueous solutions.
Partition Coefficient (n-octanol/water):	No data available.
Auto-Ignition Temperature:	No data available.
Decomposition Temperature:	No data available.
Viscosity:	No data available.

10. Stability and Reactivity

Reactivity:	No data available.
Chemical Stability:	Stable under recommended storage conditions.
Possibility of Hazardous Reactions:	No data available.

Conditions to Avoid (e.g., static discharge, shock, or vibration): No data available.

Incompatible Materials: No data available.

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

Information on the Likely Routes of Exposure:

Inhalation: Potentially irritating to the respiratory tract.

Ingestion: No data available.

Skin Contact: No data available.

Eye Contact: Potentially irritating to the eye.

Symptoms Related to the Physical, Chemical and Toxicological Characteristics: See Section 4. To the best of our knowledge, the chemical, physical and toxicological properties have not been thoroughly investigated.

Delayed and Immediate Effects of Exposure: No data available.

Acute Toxicity:

Compound	Species	Route	Type	Dose
Midazolam HCl	Rat	Oral	LD_{50}	1,600 mg/kg
Midazolam HCl	Rat	Oral	LD_{50}	215 mg/kg
Midazolam HCl	Rat	Intravenous	LD_{50}	75,357 mg/kg
Midazolam HCl	Mouse	Intravenous	LD_{50}	50 mg/kg
Midazolam HCl	Rat, Mouse	Intramuscular	LD_{50}	>50 mg/kg
Benzyl Alcohol	Rat, Mouse, Rabbit, Guinea Pig	Oral	LD_{50}	1,040 to 2,500 mg/kg
Benzyl Alcohol	Rabbit	Dermal	LD_{50}	2,000 mg/kg
Benzyl Alcohol	Rat, Mouse	Inhalation	LD_{50}	>500 mg/m^3

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.

Corrosivity:	No data available.
Dermal Irritation:	None anticipated from normal handling of this product. In clinical use, allergic reactions including anaphylactoid reactions, hives, rash, pruritus have been reported infrequently.
Eye Irritation:	None anticipated from normal handling of this product. Midazolam produced minimal eye irritation in a study in animals. However, exposure to benzyl alcohol has produced severe eye irritation in studies in animals. Inadvertent contact of this product with eyes may produce redness and discomfort.
Sensitization:	None anticipated from normal handling of this product. In clinical use, allergic reactions including anaphylactoid reactions, hives, rash, pruritus have been reported infrequently.
Toxicokinetics/Metabolism:	No data available.
Specific Target Organ Toxicity – Single Exposure:	No data available.
Specific Target Organ Toxicity – Repeat Exposure:	Based on clinical use, possible target organs include the central nervous system, gastrointestinal system, genitourinary system, cardiovascular system, and possibly the fetus.
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.
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.

National Toxicology Program (NTP):	Not considered to be a carcinogen.
International Agency for Research on Cancer (IARC):	Not considered to be a carcinogen.
Occupational Safety and Health Administration (OSHA):	Not considered to be a carcinogen.
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.
Aspiration Hazard:	None anticipated from normal handling of this product.

12. Ecological Information

Ecotoxicity

Aquatic: Not determined for this product. Information for ingredient is as follows.

Compound	Species	Type	Dose	Duration
Midazolam	Daphnia	LC_{50}	7.1 mg/l	48 Hours
Midazolam	Rainbow Trout	LC_{50}	4.3 mg/l	48 Hours
Midazolam	Algae	EbC_{50}	11.4 mg/l	72 Hours – the no-observable biological effect concentration on growth was 3.7 mg/l
Benzyl Alcohol	Pimephales promelas	LC_{50}	460 mg/L	96 Hours
Benzyl Alcohol	Leuciscus idus	LC_{50}	640 mg/L	96 Hours
Benzyl Alcohol	Daphnia magna	EC_{50}	400 mg/L	24 Hours
Benzyl Alcohol	Chlorella pyrennoidosa	EC_{50}	95 mg/L	24 Hours

Terrestrial: No data available.

Persistence and Degradability: Not determined for the product.
Information for ingredients is as follows: Midazolam was only 6% biodegraded in 28 days in the Sturm test. For midazolam, the EC_{50} (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. Benzyl alcohol was degraded over 90% in a 28-day biodegradation assay in sewage sludge.

Bioaccumulative Potential: No data available.
Mobility in Soil: No data available.
Mobility in Environment: No data available.
Other Adverse Effects: No data available.

13. Disposal Considerations

Dispose of all waste in accordance with Federal, State and Local regulations.

14. Transport Information

UN Number:	Not applicable.
UN Proper Shipping Name:	Not applicable.
Transport Hazard Class(es):	Not applicable.
Packing Group:	Not applicable.
Department of Transportation:	Not regulated as a hazardous material.
International Air Transport Association (IATA):	Not regulated as a dangerous good.
International Maritime Dangerous Good (IMDG):	Not regulated as a dangerous good.

15. Regulatory Information

US Federal Regulations:

Toxic Substance Control Act (TSCA):	Not listed.
CERCLA Hazardous Substance and Reportable Quantity:	Not listed.
SARA 313:	Not listed.
SARA 302:	Not listed.

State Regulations

California Proposition 65:	Not listed.

16. Other Information

Not made with natural rubber latex.

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