Azacitidine for injection

SAFETY DATA SHEET

Section 1: Identification

Common/Trade Name: Azacitidine for injection, 100 mg/vial
Manufacturer's Name: Shilpa Medicare Limited, Jadcherla, Telangana State, India.
Emergency Telephone Number: +91-8532-235876
Chemical Family: Antineoplastic Agents
Product Use: Pharmaceutical product used for treatment of patients with myelodysplastic syndrome

Section 2: Hazard(s) Identification

Patients/Consumers: Please refer to the product information insert or product label for appropriate consumer-specific information about this product when used according to the physician's directions. Pharmaceutical Agent – Handling of this product in its final form presents minimal occupational exposure risk.

Classification of the Substance or Mixture

Classification (GHS-US):

Comb. Dust	
Acute Tox. 4 (Oral)	H302
Carc. 1B	H350

Full text of H-phrases: see section 16

Label Elements

GHS-US labeling

Hazard pictograms (GHS-US):

GHS07 **GHS08**

Appearance: Lyophilized white powder in vial

Signal Word (GHS-US): DANGER

Hazard statements (GHS-US):

Comb. Dust - May form combustible dust concentrations in air
H302 - Harmful if swallowed
H350 - May cause cancer

Precautionary statements (GHS-US):

P201 - Obtain special instructions before use.

P202 - Do not handle until all safety precautions have been read and understood.

P264 - Wash hands, forearms and exposed areas thoroughly after handling.

P270 - Do not eat, drink or smoke when using this product.

P280 - Wear protective clothing, protective gloves, eye protection.

P301+P312 - If swallowed: Call a POISON CENTER if you feel unwell.

P308+P313 - If exposed or concerned: Get medical advice/attention.

P330 - Rinse mouth.

P405 - Store locked up.

P501 - Dispose of contents/container in accordance with local, regional, national, territorial, provincial, and international regulations.

Hazard Overview: Contains a pharmacologically active compound currently indicated for the treatment of certain myelodysplastic syndromes. The physical, chemical, and ecological properties of this material have not been fully characterized. Exposure by any route should be minimized. Exercise due care: wear suitable protective clothing, gloves and eye/face protection.

Statement of Known Hazard: Contains azacitidine: Probable human carcinogen. May cause hematological toxicity, gastrointestinal effects, fever, fatigue and ecchymosis. Potential reproductive/developmental toxicant.

Section 3: Composition / Information on Ingredients

Ingredient(s):	CAS #	% (by wt)	Classification (GHS-US)
Azacitidine	320-67-2	50%	Acute Tox. 4 (Oral), H302 Carc. 1B, H350
D-Mannitol	69-65-8	50%	Comb. Dust

Section 4: First-Aid Measures

Description of First Aid Measures

General: Never give anything by mouth to an unconscious person. If you feel unwell, seek medical advice (show the label where possible).

Inhalation: The risk of inhalation exposure is negligible when product is in its final packaged form. If

exposed and become symptomatic, move to fresh air and get medical attention if symptoms persist.

Skin Contact: Basic hygiene and appropriate precautions should prevent skin contact. If skin contact occurs, wash affected area with soap and water for at least 15 minutes. Should skin irritation, allergic reaction, or rash occur, remove contaminated clothing (if required) and seek medical advice.

Eye Contact: The risk of eye exposure is negligible when product is in its final packaged form. If eye contact occurs, flush immediately with water for at least 15 minutes. If easy to do, remove contact lenses. Get medical attention.

Ingestion: Ingestion is not an anticipated route of exposure. If accidental ingestion occurs, flush mouth out with water and get medical attention.

Most Important Symptoms and Effects Both Acute and Delayed

General: Harmful if swallowed. Please refer to the package insert for more detailed information.

Inhalation: May be harmful if inhaled.

Skin Contact: May be harmful in contact with skin.

Eye Contact: May be absorbed through the eyes.

Ingestion: Harmful if swallowed.

Injection: Not available

Chronic symptoms: May cause cancer.

Indication of Any Immediate Medical Attention and Special Treatment Needed

If exposed or concerned, get medical advice and attention. In the event of accidental injection, go immediately to the nearest emergency room.

Section 5: Fire-Fighting Measures

Extinguishing Media

Suitable extinguishing media: Use extinguishing media appropriate for surrounding fire.

Unsuitable extinguishing media: Do not use a heavy water stream. Use of heavy stream of water may spread fire.

Special Hazards Arising From the Substance or Mixture

Fire hazard: Combustible.

Explosion hazard: Product itself is not explosive but if dust is generated, dust clouds suspended in air can be explosive.

Reactivity: Hazardous reactions will not occur under normal conditions.

Advice for Firefighters

Precautionary measures fire: Exercise caution when fighting any chemical fire.

Firefighting instructions: Use water spray or fog for cooling exposed containers.

Protection during firefighting:	Do not enter fire area without proper protective equipment, including respiratory protection.
Hazardous Combustion Products:	Carbon oxides (CO, CO_2). Nitrogen compounds.
Other information:	Refer to Section 9 for flammability properties.

Section 6: Accidental Release Measures

Personal Precautions, Protective Equipment and Emergency Procedures

General measures: Avoid generating dust. Do not breathe dust. Do not get in eyes, on skin, or on clothing.

For Non-Emergency Personnel

Protective equipment: Use appropriate personal protection equipment (PPE).

Emergency procedures: Evacuate unnecessary personnel.

For Emergency Personnel

Protective equipment: Equip cleanup crew with proper protection.

Environmental Precautions Prevent entry to sewers and public waters.

Methods and Material for Containment and Cleaning Up

Methods for cleaning up: For small quantities associated with normal therapeutic use, collect spillage and transfer to a closed waste container for disposal. For large or bulk quantities, after absorption with inert material, collect spillage by sweeping up spilled material and place in a labeled, sealed container for proper disposal. Avoid generation of dust during clean-up of spills.

Reference to Other Sections

See heading 8, Exposure Controls and Personal Protection.

Section 7: Handling and Storage

Precautions for Safe Handling

Patients/Consumers:	Patients should adhere to the instructions provided within the product information insert or product label for appropriate consumer-specific information about this product when used according to the physician's directions.
Additional hazards when processed:	May form combustible dust concentrations in air.
Hygiene measures:	This SDS is for a pharmaceutical agent - Handling of this product in its final form presents minimal occupational exposure risk. In an occupational setting, handle in accordance with good industrial hygiene and safety procedures. Avoid contact with eyes, skin and clothing. Avoid breathing dust. Use appropriate

personal protective equipment when handling and observe good personal hygiene measures after handling.

Conditions for Safe Storage, Including Any Incompatibilities

Storage conditions: Store in a dry, cool and well-ventilated place. Protect from heat and direct sunlight.

Specific End Use(s)

Pharmaceutical. Refer to product insert for usage instructions and product information.

Section 8: Exposure Controls / Personal Protection

Control Parameters

For substances listed in section 3 that are not listed here, there are no established Exposure limits from the manufacturer, supplier, importer, or the appropriate advisory agency including: ACGIH (TLV), NIOSH (REL), OSHA (PEL), Canadian provincial governments, or the Mexican government.

Exposure Controls

Appropriate engineering controls: Not generally required. Site-specific risk assessments should be conducted to determine the appropriate exposure control measures. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits.

Personal protective equipment: In case of dust production: protective goggles. Gloves. Insufficient ventilation: wear respiratory protection.

Hand protection: Wear protective gloves made from PVC, neoprene, nitrile, vinyl, or PVC/NBR.

Eye protection: In laboratory, medical or industrial settings, or operations in which airborne particulates will be generated, safety glasses with side shields are recommended.

Skin and body protection: In laboratory, medical or industrial settings, impervious disposable gloves and protective clothing are recommended if skin contact with drug product is possible.

Respiratory protection: When manufacturing or handling product in large quantities and dusts or particulates may be generated, maintain airborne concentrations below recommended limits. Workplace risk assessments should be completed before specifying and implementing respirator usage. NIOSH/MSHA approved respirators for protection should be used if respirators are found to be necessary.

Section 9: Physical and Chemical Properties

The following data describe the active ingredient, azacitidine.

Physical State:	Solid
Color:	White to off-white
Molecular Formula:	C8H12N4O5
Molecular Weight:	244.2
pH:	Not available
Melting Point:	225-230°C
Solubility in Water:	Slightly soluble

Section 10: Stability and Reactivity

Reactivity:	Hazardous reactions will not occur under normal conditions.
Chemical Stability:	Stable under normal conditions.
Possibility of Hazardous Reactions:	Hazardous polymerization will not occur.
Conditions to Avoid:	Direct sunlight. Extremely high or low temperatures.
Incompatible Materials:	Strong oxidizers. Strong bases. Strong acids.
Hazardous Decomposition Products:	Carbon oxides (CO, CO2). Nitrogen compounds
Hazardous Polymerization:	Not expected to occur

Section 11: Toxicological Information

The following data describe the active ingredient, azacitidine.

Acute Toxicity:

LD50 oral, mouse: 572 mg/kg
LD10 IV, mouse: 87-199 mg/kg
LD50 IV, mouse: 117-250 mg/kg
LD10 IV, rat: 38 mg/kg
LD50 IV, rat: 51 mg/kg
LD50 IV, dog LethalIV Dose, dog 13.3 mg/kg

Repeat Dose Toxicity:

Repeat-dose toxicity studies have been conducted in mice, dogs and monkeys. The main target organs of toxicity were the bone marrow, liver, kidneys and lymphoid tissue.

5-day IV study, dog: No-observed-adverse-effect level (NOAEL) = 0.28 mg/kg/day.

14-day oral study, dog: NOAEL ≈ 0.2 mg/kg/day.
14-day IV study, monkey: A dose of 2.2 mg/kg/day caused mortality, while 1.1 mg/kg/day caused

leukopenia, anemia, elevated liver enzymes and increased BUN.

Irritation/Sensitization:
Mild skin irritation was observed when a 9% solution of azacitidine was topically applied to rabbits. No data on sensitization was identified.

Genotoxicity:
Azacitidine was a weak mutagen in several bacterial systems. It was both mutagenic and clastogenic in mammalian cell systems. Additionally, it induced mitotic recombination and mutations in *Drosophila*. Azacitidine did not induce dominant lethal mutations in mice.

Carcinogenicity:
The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumors of the hematopoietic system in female mice at 2.2 mg/kg administered IP three times per week for 52 weeks. An increased incidence of tumors of the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine IP at 2.0 mg/kg once a week for 50 weeks. A tumorigenicity study in rats dosed twice weekly at 2.5 of 10 mg/kg revealed an increased incidence of testicular tumors.

Reproductive and Developmental Toxicity:
Intraperitoneal (IP) administration of azacitidine to male mice at 3.3 mg/kg daily for 3 days prior to mating resulted in decreased fertility and loss of offspring during embryonic and postnatal development periods. Treatment of male rats three times per week for 11 or 16 weeks at IP doses of 2.5 to 5 mg/kg resulted in reduced weight of the testes and epidydimides, and decreased sperm counts accompanied by lower pregnancy rates and increased loss of embryos in mated females. In a related study, male rats treated IP for 16 weeks at 24 mg/m2 resulted in an increase in abnormal embryos in mated females when examined on day 2 of gestation.

Early embryotoxicity studies in mice revealed a ~44% frequency of intrauterine embryonic death after a single IP injection of 6 mg/m2 azacitidine on gestation day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation day 15 at ~12 mg/m2 IP. In rats, azacitidine was clearly embryotoxic when given IP on gestation days 4-8 at a dose of 6 mg/m2, although treatment earlier in gestation had no adverse effects on the embryos. Azacitidine caused multiple fetal abnormalities in rats after a single IP dose of 3 to 12 mg/m2 given on gestation day 9, 10, 11 or 12. The fetal abnormalities included: exencephaly/encephalocele, micromelia, club foot, syndactyly, oligodactyly, micrognathia, gastoschisis, edema and rib abnormalities. An increased incidence of leukemia and other malignant neoplasms has also been observed in the offspring of pregnant mice treated with azacitidine at doses lower than the human therapeutic dose.

Human Clinical Data
The recommended subcutaneous dose of azacitidine is 75 mg/m2 daily for 7 days, every 4 weeks. The most commonly occurring adverse effects with therapeutic use include hematological toxicity (*e.g.*,

thrombocytopenia, anemia, neutropenia), fever, gastrointestinal effects (*e.g.*, nausea, vomiting, diarrhea, constipation), fatigue, injection site erythema, ecchymosis (skin discoloration caused by escape of blood into tissues from ruptured blood vessels).

Azacitidine has been reported as a human skin/eye irritant. It is reasonable to assume that it may also be irritating to other mucous membranes (*e.g.*, respiratory tract).

Section 12: Ecological Information

Toxicity Not available
Persistence and Degradability Not available
Bioaccumulative Potential Not available

Section 13: Disposal Considerations

Waste disposal recommendations:	Dispose of waste material in accordance with all local, regional, national, provincial, territorial and international regulations. Do not dispose of waste into sewer.
Additional information:	Contaminated sharps should be discarded immediately or as soon as possible in containers that are closable, puncture-resistant, leak proof on sides and bottoms, and appropriately labeled. Contact your local health department for referral to a Safe Syringe Disposal Program.

Section 14: Transport Information

In Accordance With ICAO/IATA/DOT/TDG
UN Number Not regulated for transport
UN Proper Shipping Name Not regulated for transport

Section 15: Regulatory Information

US Federal Regulations

Azacitidine for Injection, 100 mg
SARA Section 311/312 Hazard Classes:
Immediate (acute) health hazard ,
Delayed (chronic) health hazard

D-Mannitol (69-65-8): Listed on the United States TSCA (Toxic Substances Control Act) inventory

US State Regulations

5-Azacytidine (320-67-2)
U.S. - California - Proposition 65 - Carcinogens List:
WARNING: This product contains chemicals known to the State of California to cause cancer

5-Azacytidine (320-67-2)

U.S. - Illinois - Toxic Air Contaminant Carcinogens
U.S. - Illinois - Toxic Air Contaminants
RTK - U.S. - Massachusetts - Right To Know List

Canadian Regulations

Azacitidine for Injection, 100 mg

WHMIS Classification: Class D Division 2 Subdivision A - Very toxic material causing other toxic effects

D-Mannitol (69-65-8)

Listed on the Canadian DSL (Domestic Substances List)

WHMIS Classification: Uncontrolled product according to WHMIS classification criteria

This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations (CPR) and the SDS contains all of the information required by CPR.

Section 16: Other Information

Revision Date:	10 Nov 2016
Data sources:	This document has been prepared in accordance with the SDS requirements of the OSHA Hazard Communication Standard 29 CFR 1910.1200.
Other information:	This document has been prepared in accordance with standards for workplace safety. The precautionary statements and warnings included might not apply in all cases. Your needs may vary depending on the potential for exposure in your workplace.

GHS Full Text Phrases:

Acute Tox. 4 (Oral):	Acute toxicity (oral) Category 4
Carc. 1B:	Carcinogenicity Category 1B
Comb. Dust:	Combustible Dust
Comb. Dust:	May form combustible dust concentrations in air
H302:	Harmful if swallowed
H350:	May cause cancer

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