MATERIAL SAFETY DATA SHEET

Section 1 – Identification of the Substance and Company

Product Name: Vidaza® (Azacitidine for injectable suspension {EU}/ Azacitidine for injection {US})
Synonyms: Mylosar, Ladakamycin

Intended Use: Formulated pharmaceutical product for human use

Company: Celgene Corporation
Address: 86 Morris Avenue
Summit, NJ 07901
(908) 673-9000
msdscoordinator@celgene.com

In case of Emergency, contact: **Chemtrec** 1-(800) 424-9300 (within USA)
(703) 527-3887 (outside USA)

Section 2 – Composition / Information on Ingredients

Ingredient(s):	CAS #	EINECS/ELINCS	% (by wt)	EU Classification
Azacitidine	320-67-2	206-280-2	50%	T; R22, R36/37/38, R45, R62, R63
D-Mannitol	69-65-8	200-711-8	50%	None required

Section 3 – Hazards Identification

Appearance: Lyophilized powder in vial.

Signal Word: None Required

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.

EU Classification: None required

Section 4 – First Aid Measures

Eye Contact
Immediately flush eyes thoroughly with water for at least 15 minutes; Seek immediate medical assistance and notify supervisor.

Skin Contact
Remove all contaminated clothing and rinse area thoroughly with soap and water for 15 minutes; Seek immediate medical assistance and notify supervisor.

Inhalation
Remove from exposure source; notify medical personnel and supervisor if breathing difficulties develop. Administer artificial respiration if necessary.

Ingestion
Seek immediate medical assistance. Do not induce vomiting, give liquids, or use any other method to remove poison unless advised by physician or Poison Control.

Medical Conditions Aggravated by Exposure
No information available.

Notes to Physician
Formulated product contains azacitidine, a cytotoxic analog of the naturally occurring pyrimidine nucleoside, cytidine. Azacitidine is a probable human carcinogen and may cause hematological toxicity, gastrointestinal effects, fever, fatigue and ecchymosis. Potential reproductive/developmental toxicant. (see section 3 and 11 for more details).

Section 5 – Fire Fighting Measures

Flammability/Explosivity
Not considered to be a fire hazard. No explosivity data available.

Extinguishing Media
Use suitable extinguishing media (*e.g.*, water, alcohol foam, dry chemical, CO_2).

Special Fire Fighting Procedures
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.

Hazardous Combustion Products
Carbon monoxide, nitrogen oxides

Section 6 – Accidental Release Measures

If vial is crushed or broken, dust containing drug substance may be released. Minimize dust generation and accumulation. Do not breathe dust.

Spill Protection Equipment
For large spills wear a respirator or other device that will protect you from dust or aerosols raised during the spill. Wear safety goggles, water-resistant coveralls, rubber boots and heavy rubber gloves.

Procedures to be Followed in Case of Leak or Spill

Do not raise dust. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize powder from entering the air. Add excess liquid to allow for the material to enter solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container suitable for disposal. Decontaminate area a second time. Dispose of material in a manner that is compliant with federal, state and local laws.

Section 7 – Handling and Storage

Storage
Store in a dark, well-ventilated area away from sources of ignition and incompatible materials. Protect against physical damage and keep containers tightly sealed. Store at 25°C, with excursions permitted in the range of 15-30°C.

Other Precautions
Follow recommendations for handling pharmaceutical agents (i.e., use of engineering controls and/or other personnel protective equipment if needed). Wash thoroughly after handling.

Section 8 – Exposure Controls / Personal Protection

If vials are broken, dust containing drug substance may be released. Minimize dust generation and accumulation. Do not breathe dust.

Occupational Exposure Limit / Occupational Exposure Category or Band

The following information is for components of the formulated product.

None currently established by OSHA, ACGIH or NIOSH.

Celgene has adopted an $OEL_{8hr\text{-}TWA}$ of 0.5 µg/m^3 for azacitidine.

Engineering Controls
When practicable, handle material in enclosed processes or in processes with effective and well-engineered local exhaust ventilation. The emphasis of control should be no open handling and containment and control at the source of dust or aerosol generation. For re-constitution, powder should be handled in a barrier isolator, ventilated enclosure, or other equivalent containment device.

Eye 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.

Respiratory Protection
- When possible, handle material in enclosed processes or containers. In the laboratory, if it is properly handled with effective containment, respiratory protection may not be needed.
- If conducting activities outside of containment where there is a potential for aerosolization of the drug product, use of an air-purifying respirator with NIOSH/MSHA approval for dusts and mists should be considered. The use of respiratory protection should be appropriate for the job activity being conducted.

Skin Protection
Rubber (latex) or nitrile gloves are recommended to minimize potential for skin contact when handling in dry form or in aqueous solutions. Double gloves should be considered. When the material is dissolved in an organic solvent, wear gloves that provide protection against the solvent. Wear lab coat or other protective overgarment. Base the choice of protection on the job activity and potential for skin contact.

Other
Wash hands, face and other potentially exposed areas immediately after handling material (especially before eating, drinking, or smoking). Decontaminate all protective equipment after use. Always exercise extreme care when working with sharps/needles/syringes and potent drugs.

Section 9 – Physical and Chemical Properties

Physical State: Lyopholized powder in vial

The following data describe the active ingredient, azacitidine.

Physical State:	Solid
Color:	White to off-white
Molecular Formula:	$C_8H_{12}N_4O_5$
Molecular Weight:	244.2
pH:	Not available
Boiling Point:	Not available
Melting Point:	225-230°C
Vapor Pressure:	Not available
Solubility in Water:	Slightly soluble
Evaporation Rate:	Not available
Specific Gravity:	Not available
Vapor Density:	Not available
Percent Volatile:	Not available

Section 10 – Stability and Reactivity

Stability:	Rapid decomposition in neutral or alkaline solutions
Hazardous Polymerization:	Not expected to occur
Hazardous Decomposition Products:	None known
Conditions to Avoid:	Avoid heat and sunlight
Materials to Avoid:	Strong oxidizing agents

Section 11 – Toxicological Information

The following data describe the active ingredient, azacitidine.

Acute Toxicity:

LD_{50} oral, mouse:	572 mg/kg
LD_{10} IV, mouse:	87-199 mg/kg
LD_{50} IV, mouse:	117-250 mg/kg
LD_{10} IV, rat:	38 mg/kg
LD_{50} IV, rat:	51 mg/kg
LD_{50} 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/m^2 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/m^2 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/m^2 IP. In rats, azacitidine was clearly embryotoxic when given IP on gestation days 4-8 at a dose of 6 mg/m^2, 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/m^2 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/m^2 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 – Environmental Information

No studies identified.

Section 13 – Disposal Considerations

All wastes containing the material should be properly labeled. Dispose of wastes in accordance with prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. 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

Hazard Class: Not regulated

UN Number: None assigned

Section 15 – Regulatory Information

This MSDS complies with the requirements under 29 CFR 1910.1200 and EU guidelines.

OSHA Label
Probable human carcinogen. May cause hematological toxicity, gastrointestinal effects, fever, fatigue and ecchymosis. Potential reproductive/developmental toxicant.

Containers of this material should have affixed the following label (in addition to the identity label):

> **Caution:** Contains a pharmacologically active compound. Probable human carcinogen. May cause hematological toxicity, gastrointestinal effects, fever, fatigue and ecchymosis. Potential reproductive/developmental toxicant. Exposure by any route should be minimized. Read and understand the Material Safety Data Sheet before handling material.

EU Indication of Danger: None Required
EU Risk Phrases: None Required
EU Safety Phrases: None Required

Canada – WHMIS Classifications
None required

California Proposition 65:	Azacitidine - Listed as carcinogen.
SARA 313:	Not listed.
CERCLA :	Not listed.
RCRA:	Not listed.
TSCA:	Not listed.
NTP:	Azacitidine -Reasonably anticipated to be a human carcinogen
IARC:	Azacitidine -Group 2A (Probably carcinogenic to humans)
NIOSH:	Azacitidine -Listed as a hazardous drug
Other:	Azacitidine -Listed as hazard communication carcinogen under OSHA.

Section 16 – Other Information

Abbreviations from Sections 2, 3 and 15
R22 Harmful if swallowed

R36/37/28	Irritating to eyes, respiratory system and skin
R45	May cause cancer
R62	Possible risk of impaired fertility
R63	Possible risk harm to the unborn child

T - Toxic

Sources of Key Data Used to Compile MSDS
Information from published literature, Investigator's Brochure, previous versions of MSDS

This MSDS supersedes the previous Pharmion version 2.0.

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 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 Material Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.

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