SAFETY DATA SHEET

SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/ UNDERTAKING

Contact information

General

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Product identifier

Vidaza®

Synonyms

Mylosar, Ladakamycin

Trade names

Vidaza® powder for suspension for injection; azacitidine for injection

Chemical family

Mixture - contains pyrimidine nucleoside analog

Relevant identified uses of the substance or mixture and uses advised against

Bulk formulated pharmaceutical product/ Formulated pharmaceutical product packaged in final form for patient use; indicated for the treatment of certain myelodysplastic syndromes.

Note

The physical, chemical and ecological properties of this material and/or its ingredients have not been fully characterized. This SDS will be revisited as more data become available.

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture

Drugs in the finished state and intended for the final user are not subject to labeling in the US, EU or Canada. Please consult the prescribing/packaging information. **The classification and labelling listed below is for bulk Vidaza.**

Globally Harmonized System [GHS]

Carcinogenic - Category 1B. Germ Cell Mutagenicity - Category 2. Reproductive Toxicity - Category 1B. Acute toxicity - oral - Category 4. Specific Target Organ Toxicity (repeated exposure) - Category 1. Aquatic toxicity (acute) - Category 1. Aquatic toxicity (chronic) - Category 1.

Label elements

GHS hazard pictogram

GHS signal word

Danger

GHS hazard statements

H302 - Harmful if swallowed. H341 - Suspected of causing genetic defects. H350 - May cause cancer. H360FD - May damage fertility. May damage the unborn child. H372 - Causes damage to hematological and gastrointestinal systems through prolonged or repeated exposure. H400 - Very toxic to aquatic life. H410 - Very toxic to aquatic life with long-lasting effects.

GHS precautionary statements

P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. P260 - Do not breathe dust. P264 - Wash hands thoroughly after handling. P270 - Do not eat, drink or smoke when using this product. P273 - Avoid release to the environment. P281 - Use personal protective equipment as required. P308 + P313 - If exposed or concerned: get medical advice/attention. P301+P312: IF SWALLOWED: Call a Poison Center or doctor/physician if you feel unwell. P330 - Rinse mouth. P391 - Collect spillage. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations. P280 - Wear protective gloves/eye protection/face protection. P308 + P313 - IF exposed or concerned: get medical advice/attention.

Other hazards

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). Other effects may include hypotension, shortness of breath, liver/kidney toxicity and electrolyte abnormalities. Post-marketing reports of interstitial lung disease and tumor lysis syndrome may also be azacitidine-related.

Note

This mixture is classified as hazardous under GHS as implemented by Regulation EC No 1272/2008 (EU CLP), WHMIS 2015 (Health Canada), and Hazard Communication Standard No. 1910.1200 (US OSHA). See Section 16 for full text of EU and GHS classifications.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	GHS Classification
Azacitidine	320-67-2	206-280-2	50%	ATO4: H302; Carc1B: H350; STOT-R1: H372; RT1B: H360FD; GCM2: H341; AA1: H400; CA1: H410

Note The ingredient(s) listed above are considered dangerous/hazardous. The remaining components are non-dangerous/not hazardous and/or present at amounts below reportable limits. See Section 16 for full text of GHS classifications.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures

Immediate Medical Attention Needed Yes

Eye Contact If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.

Skin Contact Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.

Inhalation Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.

Ingestion Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.

Protection of first aid responders See Section 8 for Exposure Controls/Personal Protection recommendations.

Most important symptoms and effects, both acute and delayed See Sections 2 and 11.

Indication of immediate medical attention and special treatment needed, if necessary Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective package or prescribing information for potential drug interactions.

SECTION 5 - FIREFIGHTING MEASURES

Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Specific hazards arising from the substance or mixture	No information identified. May emit carbon monoxide, carbon dioxide, and oxides of nitrogen.
Flammability/ Explosivity	Not considered to be a fire hazard. No explosivity data available. High concentrations of finely divided airborne organic particles can potentially explode if ignited.
Advice for firefighters	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.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe dust.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	If vials are broken or crushed, DO NOT RAISE DUST. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize entry of powder into the air. Add excess liquid to allow the material to enter solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container suitable for disposal in accordance with applicable waste disposal regulations (see Section 13). Decontaminate the area twice.
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	If vials are crushed or broken, dust containing drug substance may be released. Minimize dust generation and accumulation. Follow recommendations for handling bulk formulated/packaged cytotoxic pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling. Avoid breathing dust.
Conditions for safe storage including any incompatibilities	Store at controlled room temperature (25°C) away from incompatible materials. Excursions are permitted to 15-30°C. Keep away from children. Store locked up.
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Azacitidine	Celgene	TWA-8 HR	1 µg/m³

DNELs/PNECs

Azacitidine: PNEC (water) - 1.2 µg/L; PNEC (microorganism) - >1000 µg/L; PNEC (groundwater) - 73 µg/L.

Exposure/Engineering controls

If handling bulk product or vials are crushed/broken: Open handling should not be performed when handling potent substances or substances of unknown toxicity. Control exposures to below the OEL (if available). Otherwise, selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for dusts and/or aerosols.

Respiratory protection

If handling bulk product or vials are crushed/broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine powder handling tasks, an approved and properly worn powered air-purifying respirator equipped with HEPA filters or combination filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a positive-pressure air-supplied respirator if there is any potential for an uncontrolled release, when exposure levels are not known, or in any other circumstances where air purifying respirators may not provide adequate protection.

Hand protection

Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered. When the material is dissolved or suspended in an organic solvent, wear gloves that provide protection against the solvent.

Skin protection

Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.

Eye/face 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. An emergency eye wash station should be available.

Environmental Exposure Controls

Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.

Other protective measures

Wash hands in the event of contact with this substance, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Lyopholized powder/Lyopholized powder in vial
Color	White to off-white
Odor	No information identified.
Odor threshold	No information identified.
pH	No information identified.
Melting point/ freezing point	~225-230°C (azacitidine)
Initial boiling point and boiling range	No information identified.
Flash point	No information identified.
Evaporation rate	No information identified.
Flammability (solid, gas)	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	No information identified.
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	14 mg/mL (azacitidine)
Solvent solubility	Insoluble in acetone, ethanol, and methyl ethyl ketone; Soluble in dimethylsulfoxide (azacitidine)
Partition coefficient (*n-octanol/water*)	-0.1-0.2 at pH 2 and 12 (25°C) (azacitidine)
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Other information

Molecular formula $C_8H_{12}N_4O_5$ (azacitidine)

Molecular weight 244.2 (azacitidine)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity No information identified.

Chemical stability Rapid decomposition in neutral or alkaline solutions; pharmacological stability not guaranteed beyond expiration date imprinted on package.

Possibility of hazardous reactions Not expected to occur.

Conditions to avoid Avoid extreme temperatures. Avoid direct sunlight.

Incompatible materials No information identified.

Hazardous decomposition products No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note **The following data describe the active ingredient, azacitidine.**

Information on toxicological effects

Route of entry May be absorbed by inhalation, skin contact and ingestion.

Acute toxicity

Compound	Type	Route	Species	Dose
Azacitidine	LD_{50}	Oral	Mouse	572 mg/kg
	LD_{50}	IV	Mouse	~117 mg/kg
	LD_{50}	IV	Rat	~51 mg/kg
	Approximate lethal dose	IV	Dog	~13.3 mg/kg

Irritation/Corrosion Mild skin irritation was observed when a 9% solution of azacitidine was topically applied to rabbits.

Sensitization No data available.

STOT-single exposure Single IV administration of azacitadine to dogs at doses of 3.32 and 6.65 mg/kg caused only reversible hematological changes and liver enzyme increases.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

STOT-repeated exposure/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, kidney, lymphoid tissue, and the gastrointestinal tract.

14-day oral study, dog: Maximum tolerated dose (MTD) = 0.2 mg/kg/day.
10-day (5 days x 2 cycles) IV study, dog: MTD = 0.55 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.

Reproductive toxicity

In rodents treated with low intraperitoneal (IP) doses, azacitidine has produced adverse effects on male reproduction and fertility, including decreased testes/epididymis weights, decreased sperm counts and decreased pregnancy rates.

Developmental toxicity

Azacitidine produces dose-dependent embryotoxicity/embryolethality and teratogenicity in rodents after IP administration of doses as low as 1-2 and 0.5 mg/kg, respectively.

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

Azacitidine has shown carcinogenic potential in rodents following IP administration. Azacitidine has been classified by the International Agency for Research on Cancer (IARC) as an IARC Group 2A carcinogen (probably carcinogenic to humans). According to NTP, azacitidine is reasonably anticipated to be a human carcinogen. Azacitidine is also listed as a carcinogen under OSHA.

Aspiration hazard

No data available.

Human health data

See "Section 2 - Other Hazards"

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Azacitidine	EC_{50}	Activated sludge	>100,000 µg/L
	EC_{50}/72h	Algae	~0.1-1.0 mg/L
	NOEC (growth rate reduction)	Algae	31 µg/L
	EC_{50}/72h (growth rate reduction)	Desmodesmus subspicatus	9.6 mg/L
	NOEC (growth rate reduction)	Desmodesmus subspicatus	0.53 mg/L

SECTION 12 - ECOLOGICAL INFORMATION …continued

Toxicity …continued

Compound	Type	Species	Concentration
	NOEC/21 days (reproduc-tion)	Daphnia magna	730 µg/L
	NOEC (Fish early life stage test)	Fathead minnow	1000 µg/L
	NOEC/7 day (growth inhibition)	Lemna minor	0.068 mg/L
	EC_{50}/7d (growth rate reduction)	Lemna minor	1.8/2 mg/L (frond numbers/wet weight)

Persistence and Degradability Azacitidine is biodegradable, but does not meet the criteria for "rapid biodegradability".

Bioaccumulative potential Based on the octanol/water partition coefficient, azacitidine is unlikely to bioaccumulate.

Mobility in soil Azacitidine is not stable in water. It is not expected to significantly adhere to sediment.

Adsorption coefficient (Koc) <33 L/kg

Results of PBT and vPvB assessment Not performed.

Other adverse effects No data available.

Note Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods Dispose of wastes by appropriately permitted chemical waste incinerator in accordance to prescribed federal, state, and local guidelines. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, *e.g.*, appropriately permitted municipal or onsite wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

Transport	Based on the available data, this packaged product is not regulated as a hazardous material/dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG. It is exempt because it is packaged in either single packages or inner packaging in combination packages containing net quantities of less than 5 kg/5 L (IMDG Code 2.10.2.7; ICAO Special Instruction A197, 49CFR 171.4(c)(2)). Shipment may be regulated if contents are removed from inner packaging and combined into containers exceeding 5 L or 5 kg. **The following regulations apply to the bulk product:**
UN number	UN3077
UN proper shipping name	Azacitidine
Transport hazard classes and packing group	Hazard Class - 9; Packing Group III.
US DOT shipping description	UN/ID Number - UN3077; Proper Shipping Name - Environmentally Hazardous Substance, Solid, n.o.s. (contains azacitidine); Hazard Class - 9; Packing Group III. (exceptions from Environmentally Hazardous Substance marking exists for certain package sizes) Sealed articles containing less than 5 kg of product can be shipped as Not Regulated under the provisions of 49 CFR 171.4.
IATA/ICAO shipping description	UN/ID Number - UN3077; Proper Shipping Name - Environmentally Hazardous Substance, Solid, n.o.s. (contains azacitidine); Hazard Class - 9; Packing Group III. (exceptions from Environmentally Hazardous Substance marking exists for certain package sizes) Sealed articles containing less than 5 kg of product can be shipped as Not Regulated per Special Provision A197.
IMDG shipping description	UN/ID Number - UN3077; Proper Shipping Name - Environmentally Hazardous Substance, Solid, n.o.s. (contains azacitidine); Hazard Class - 9; Packing Group III. (exceptions from Marine Pollutant marking exists for certain package sizes) (Marine Pollutant) Sealed articles containing less than 5 kg of product can be shipped as Not Regulated per Code 2.10.2.7.
IMDG marine pollutant	Azacitidine

SECTION 14 - TRANSPORT INFORMATION …continued

ADR Shipping Description	UN/ID Number - UN3077; Proper Shipping Name - Environmentally Hazardous Substance, Solid, n.o.s. (contains azacitidine); Hazard Class - 9; Packing Group III. Sealed articles containing less than 5 kg of product can be shipped as Not Regulated per Special Provision 375.
Canadian TDG	UN/ID Number - UN3077; Proper Shipping Name - Environmentally Hazardous Substance, Solid, n.o.s. (contains azacitidine); Hazard Class - 9; Packing Group III. (exceptions from Environmentally Hazardous Substance marking exists for certain package sizes) Sealed articles containing less than 5 kg of product can be shipped as Not Regulated per Schedule 1.
Environmental hazards	Based on the available data, this substance is regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Avoid release to the environment.
Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	Not applicable.

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS generally complies with the requirements listed under current guidelines in the US, EU and Canada. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
TSCA status	Not listed
SARA section 313	Not listed.
California proposition 65	Azacitidine is listed as a carcinogen.
Additional information	Azacitidine is listed as a hazardous drug by NIOSH.

SECTION 16 - OTHER INFORMATION

Full text of H phrases and GHS classifications	ATO4 - Acute Toxicity (Oral) Category 4. Carc1B - Carcinogenicity Category 1B. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. RT1B - Reproductive toxicity Category 1B. GCM2 - Germ Cell Mutagenicity Category 2. AA1- Acute aquatic toxicity Category 1. CA1 - Chronic Aquatic Toxicity Category 1. H302 - Harmful if swallowed. H341 - Suspected of causing genetic defects. H350 - May cause cancer. H360FD - May damage fertility. May damage the unborn child. H372 - Causes damage to hematological and gastrointestinal systems through prolonged or repeated exposure. H400 - Very toxic to aquatic life. H410 - Very toxic to aquatic life with long lasting effects.
Sources of data	Information from published literature and internal company data.
Abbreviations	ACGIH - American Conference of Governmental Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; CLP - Classification, Labelling, and Packaging of Substances and Mixtures; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STOT - Specific Target Organ Toxicity; STEL - Short Term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System
Issue Date	3 April 2017
Revisions	Updated transport regulations in Section 14. Updated general format for compliance with most recent regulatory requirements in the US, EU, and Canada.
Disclaimer	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

Disclaimer …continued

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