# MATERIAL SAFETY DATA SHEET

**Version No:** MSDS/Aza-AUS/DP-003 **Effective Date:** 11th September 2019

**AZACITIDINE FOR INJECTION 100 MG/VIAL**

## SECTION 1 – PRODUCT AND COMPANY IDENTIFICATION

**Product Name:** Azacitidine for Injection 100 mg/vial

| Sponsor | Manufacturer |
|---|---|
| Accord Healthcare Pty Ltd<br>Level 24, 570 Bourke Street<br>Melbourne, VIC, 3000<br>Australia | Intas Pharmaceuticals Ltd.<br>Plot No. 5, 6 and 7, Pharmez,<br>Near Matoda Village,<br>Ahmedabad-382 213, Gujarat, India |

## SECTION 2 – COMPOSITION, INFORMATION ON INGREDIENTS

**Active:** Azacitidine.

**Inactive:** Mannitol, Water for Injection.

| 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 3 - HAZARDS IDENTIFICATION

**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 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 3 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 - FIRE FIGHTING 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 face piece 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 leakproof 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 | Type | OEL |
|---|---|---|
| Azacitidine | 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. |
| **Other information** | **:** | |
| **Molecular formula** | **:** | C8H12N4O5 (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 - TOXICOLOGY 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 | LD50 | Oral | Mouse | 572 mg/kg |
| | LD50 | IV | Mouse | ~117 mg/kg |
| | LD50 | 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.

**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 3 - Other Hazards"

## SECTION 12 - ENVIRONMENTAL IMPACT INFORMATION

**Toxicity:**

| Compound | Type | Species | Concentration |
|---|---|---|---|
| Azacitidine | EC50 | Activated sludge | >100,000 µg/L |
| | EC50/72h | Algae | ~0.1-1.0 mg/L |
| | NOEC (growth rate reduction) | Algae | 31 µg/L |
| | EC50/72h (growth rate reduction) | Desmodesmus subspicatus | 9.6 mg/L |
| | NOEC (growth rate reduction) | Desmodesmus subspicatus | 0.53 mg/L |
| | NOEC/21 days (reproduction) | 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 |
| | EC50/7d (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 INFORMATION

**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 - TRANSPORTATION 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

**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 DATA

**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. |

**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 |

**Sources of data:** Information from published literature.

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