One case of overdose with Azacitidine for Injection was reported during clinical trials. A patient experienced diaphoresis, nausea, and vomiting after receiving a single 7.5 mg (150 mg/m²) dose of Azacitidine for Injection, 4 times the recommended starting dose. The event resolved without sequelae, and the patient continues to participate in the study. In the event of overdosage, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for Azacitidine overdosage.

**OVERDOSE**

**Route of Administration:** Subcutaneous or Intravenous

**Compatibility:** Azacitidine for Injection is compatible with normal saline and Ringer’s solution.

**Contraindications:** Azacitidine is contraindicated in patients with known history of hypersensitivity to Azacitidine.

**Pharmacokinetics**

- **Absorption:** Azacitidine is rapidly absorbed after subcutaneous administration. The mean time to peak concentration (Tmax) after subcutaneous administration is 48 ± 12 minutes. The mean systemic availability (F) after subcutaneous administration is 39 ± 27%.

- **Distribution:** Azacitidine distributes rapidly into the extracellular fluid. The mean volume of distribution (Vd) after intravenous administration is 30 ± 12 L/hour.

- **Elimination:** Azacitidine is eliminated primarily by renal excretion. The mean elimination half-life (t1/2) after intravenous administration is 4.8 ± 1.5 hours. Less than 1% of the administered dose is excreted in the feces.

**Dosage and Administration**

- **Azacitidine for Injection is supplied as a lyophilized powder in 100 mg single-dose vials.

**Intravenous Administration**

- **Volume of Administration:** Intravenous administration is recommended for patients with renal impairment or those who are unable to receive subcutaneous therapy.

**Side Effects**

- **Hematologic:** The most commonly reported hematologic adverse reactions associated with Azacitidine treatment included anemia, thrombocytopenia, neutropenia, leucopenia, and thrombocytopenia.

- **Non-Hematologic:** The most commonly reported gastrointestinal adverse reactions associated with Azacitidine treatment included constipation, diarrhea, nausea, and vomiting.

- **Drug Interactions:** Azacitidine may interact with other medications that are eliminated by the kidneys. Patients on concomitant therapy should be monitored for changes in their clinical status.

**Special Handling and Disposal**

- **Storage and Handling:** Azacitidine for Injection should be stored at room temperature (5°C to 30°C), protected from light. Once reconstituted, the solution should be used within 24 hours.

- **Disposal:** Azacitidine for Injection should be disposed of according to institutional guidelines and recommendations for the disposal of cytotoxic agents.
Serum creatinine is the first choice. Subsequent Treatment Cycles
Repeat every 4 weeks
The dose may be increased to 150 mg/m² if no beneficial effect is seen after 2 treatment cycles and if no toxicity other than mucositis is noted. It is recommended that the treatment be continued for a minimum of 4 to 6 cycles. However, complete or partial response may require further treatment, and the treatment should be continued as long as the patient continues to benefit. Management of hematologic and non-hematologic toxicities and delays or dose reductions are necessary as described below.

Dosage Adjustment Based on Hematology Laboratory Values
For patients with leukocytopenia, ANC < 1.5 x 10⁹/L, or platelets < 75 x 10⁹/L, adjust the dose as follows, based on nadir counts for the prior cycle:

- Neutropenia
  - ANC (x10⁹/L)
    - <0.5
    - 0.5 to 1.5
    - >1.5
  - % Dose in the Next Cycle
    - 60
    - 50
    - 40

- Platelet Count
  - Platelets (x10⁹/L)
    - <25
    - 25 to 50
    - 50 to 75
    - >75
  - % Dose in the Next Cycle
    - 40
    - 50
    - 60
    - 70

For patients whose baseline counts are WBC < 3.0 x 10⁹/L, ANC < 1.5 x 10⁹/L, or platelets < 75 x 10⁹/L, base dose adjustments on nadir counts and bone marrow morphology are recommended. For patients whose nadir counts are within the range of normal values, leukocyte counts and ANC are higher than the lower limit of expected counts for the time of the next cycle, in which case the current dose is continued.

Dosage Adjustment Based on Serum Electrolytes and Renal Toxicity
If unexplained reductions in serum bicarbonate levels < 19 mg/dL occur; reduce the dose of gemcitabine by 20% in the next cycle. Similarly, if unexplained elevations of BUN or serum creatinine occur, the dose may be reduced by 20% for the next course.

Use in Geriatric Patients
Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the renal clearance of azacitidine may be reduced in elderly patients with impaired renal function. Therefore, elderly patients are more likely to have decreased renal function and may require dose reductions. The dose should be carefully monitored and renal function reduced.

Method of Preparation
Azacitidine is a cyanosemic drug. Procedures for proper handling and disposal should be used.

Intravenous Injection for Injection is a single-dose vial and does not contain any preservatives. Discard unused portions.

Intravenous Route of Administration
This drug should be administered over at least 1 hour. More rapid dosing may result in nephrotoxicity.

Intramuscular Route of Administration
There is no recommended route of administration. Use the intravenous route of administration for all patients. Intravenous administration is preferred because it prevents extravasation injury and allows for higher dosing of gemcitabine.

Intradermal Route of Administration
To administer the drug subcutaneously, the contents of the dosage vial must be reconstituted immediately prior to administration. To suspend, vigorously shake the vial and administer over a period of 1 to 2 minutes using a 21-gauge needle. If the suspension is not reconstituted immediately, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Subcutaneous Administration
Excessively high doses can result in hematologic toxicities, the contents of the dosing vial must be reconstituted immediately prior to administration. To suspend, vigorously shake the vial and administer over a period of 1 to 2 minutes using a 21-gauge needle. If the suspension is not reconstituted immediately, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Acute Toxicity
Acute toxicity is generally manifested as a dose-related increase in myelosuppression, nausea, vomiting, and diarrhea. Nausea and vomiting may be severe, leading to dehydration and electrolyte disturbances.

Dosage Adjustment Based on Toxicity
Intravenous Inflammation
Amp.P/S

Table 1: ADRs reported in patients with MDS or AML treated with azacitidine (clinical studies and post-marketing)

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Adverse reactions are generally mild to moderate in severity and may be managed with supportive care, including hydration, electrolyte replacement, and antiemetic therapy.

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