Drug Monograph

A - Drug Name

azaCITIDine

COMMON TRADE NAME(S): Vidaza®

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B - Mechanism of Action and Pharmacokinetics

Azacitidine is a pyrimidine nucleoside analogue of cytidine, which exerts cytotoxic effects by direct cytotoxicity on abnormal bone marrow cells. In addition to its incorporation into RNA/DNA and inhibition of DNA, RNA, and protein synthesis, azacitidine also inhibits DNA methylation, which may restore normal function to certain tumour suppressor genes affecting cell proliferation and differentiation. Non-proliferating cells are relatively insensitive to azacitidine.

Absorption	T max	30 min (subcut)
	Bioavailability	89% (subcut)
Distribution	Widely distributed into tissues. Drug uptake into tumour tissues (lymphoid tissues > parenchymal organs) is higher than uptake into normal tissues.	
	Cross blood brain barrier?	No information found
	PPB	6-12% (oral tablets)
Metabolism	Metabolism of azacitidine is by spontaneous hydrolysis and deamination mediated by cytidine deaminase. It does not appear to be mediated by cytochrome P450 isoenzymes.	
	Inactive metabolites	Yes

Elimination	Primarily via kidney.	
	Feces	< 1%
	Urine	50% (subcut)
	Half-life	41 minutes (subcut; mean)

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C - Indications and Status

Health Canada Approvals:

- Myelodysplastic Syndrome (MDS)
- Acute Myeloid Leukemia (AML)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: None

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (rare)	E
	Heart failure (rare)	E
	Hypertension (9%)	E
	Hypotension (7%)	E
	Venous thromboembolism (rare)	E
Dermatological	Other - acute febrile neutrophilic dermatosis, pyoderma gangrenosum (rare)	E
	Rash (14%) (or skin effects)	E

Gastrointestinal	Abdominal pain (13%)	E
	Anorexia, weight loss (21%)	E
	Constipation (50%)	E
	Diarrhea (36%)	E
	Dyspepsia (6%)	E
	GI perforation (rare)	E
	Mucositis (8%)	E
	Nausea, vomiting (71%)	I E
General	Differentiation syndrome (rare)	E D
	Fatigue (24%)	E
Hematological	Myelosuppression ± infection, bleeding (70%) (61% severe; rarely hemorrhagic diathesis)	E
Hepatobiliary	↑ LFTs (may be severe)	E
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (<1%)	I
Infection	Necrotizing fasciitis (rare)	E
Injection site	Injection site reaction (43%) (may be severe)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (6%) (↓ K)	E
	Hyperglycemia (rare)	E
	Tumor lysis syndrome (rare)	I
Musculoskeletal	Musculoskeletal pain (22%)	E
Nervous System	Anxiety (13%)	E
	Confusion (<10%)	E
	Dizziness (19%)	E
	Headache (22%)	E
	Insomnia (11%)	E
	Seizure (rare)	E
Renal	Renal failure (rare, may be severe)	E
	Renal tubular acidosis (rare)	E
Respiratory	Dyspnea (29%)	E
	Pneumonitis (rare)	E D
Vascular	Vasculitis (leucocytoclastic) (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for azaCITIDine include nausea, vomiting, myelosuppression ± infection, bleeding, constipation, injection site reaction, diarrhea, dyspnea, fatigue, headache, musculoskeletal pain, anorexia and weight loss.

Side effects tended to be more pronounced during the first 2 cycles of subcut azacitidine treatment.

Differentiation syndrome, which may be fatal, has been reported during post-marketing with azacitidine for injection. Symptoms may include the following: fever, rash, respiratory distress, pulmonary infiltrates, pulmonary or peripheral edema, pleural or pericardial effusions, rapid weight gain, hypotension and renal dysfunction.

Severe **renal** tubular dysfunction may be manifested by hypophosphatemia, hypokalemia, hyponatremia, with or without increases in creatinine and BUN. Other renal abnormalities such as tubular acidosis, elevated serum creatinine / BUN, and renal failure (including deaths) have also occurred with azacitidine treatment.

Severe **hepatic** failure has been reported in patients with extensive disease and hypoalbuminemia.

Injection site necrosis has been observed rarely. Rare cases of necrotizing fasciitis (including deaths) have been reported.

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (e.g., some leukemias and lymphomas), can be minimized with allopurinol and hydration. In hospitalized patients, the urine may be alkalinized by addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Azacitidine for injection is **not interchangeable** with, and should not be substituted with or for, azacitidine tablets. Verify drug name, dose, and administration route. The different dosage forms are not bioequivalent.

Patients should receive prophylactic antiemetics.

Consider appropriate prophylaxis and close monitoring for patients at risk of tumour lysis syndrome (i.e. high tumour burden).

Consider the use of supportive measures such as prophylactic antibiotics, transfusion and/or growth factors, according to local practice.

Adults:

Subcutaneous: (Q28 Days) 75 mg/m² Daily for 7 days

Dosage with Toxicity:

Non-hematologic:

Toxicity	Action
Differentiation syndrome	If suspected, initiate high-dose IV corticosteroids and hemodynamic monitoring. Consider temporary hold of azacitidine until symptoms resolve; resume with caution.
Necrotizing fasciitis	Discontinue
Renal tubular acidosis (low serum bicarbonate, increasing creatinine)	Reduce or delay next dose
Other severe drug related toxicity	Consider dose reduction or discontinue

Hematologic:

Normal baseline counts (X 10^9/L; WBC ≥ 3 and ANC ≥ 1.5 and platelets ≥ 75), Table 1:

Nadir Counts			% Dose in the next cycle
ANC (X 10^9/L)		Platelets (X 10^9/L)	
≤ 1	and/or	≤ 50	Delay until recovery* then 50% if recovery requires > 14 days
> 1	and/or	> 50	Delay until recovery* then 100%

*Recovery = Counts ≥ Nadir count + (0.5 x {Baseline count – Nadir count})

Low baseline counts (X 10^9/L; WBC < 3 or ANC < 1.5 or platelets < 75), Table 2:

↓ ANC or WBC or platelets from baseline		Improvement in any cell line differentiation?	Action	Recovery* within 14 days?	Action
< 50%			Treat on time with no ↓ in dose	N/A	N/A
> 50%	And	Yes	Treat on time with no ↓ in dose	N/A	N/A
> 50%	And	No	Hold until recovery*	Yes	No ↓ in dose
> 50%	And	No	Hold until recovery*	No	Check marrow cellularity (Table 3)

*Recovery = Counts ≥ Nadir count + (0.5 x {Baseline count – Nadir count})

Table 3:

Bone marrow cellularity (Refer to Table 2)	Action and % Dose in next cycle if recovery* is not achieved within 14 days	
	Recovery ≤ 21 days	Recovery > 21 days
> 50%	No dose adjustment needed	
15 – 50%	Hold until recovery*; 100%	Hold until recovery*; 50%
< 15%	Hold until recovery*; 100%	Hold until recovery*; 33%

*Recovery = Counts ≥ Nadir count + (0.5 x {Baseline count – Nadir count})

Dosage with Hepatic Impairment:

Treat with caution. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours and has not been studied in patients with hepatic impairment.

Dosage with Renal Impairment:

Monitor patients with renal impairment closely as azacitidine and its metabolites are primarily excreted renally. Azacitidine can be administered to patients with renal impairment without initial dose adjustment. Subsequent dosage modifications should be made if reductions in serum bicarbonate levels and/or elevations in serum creatinine or BUN occur. The following are suggested modifications.

Creatinine / BUN		Serum bicarbonate (mmol/L)	Action and Dose (% previous dose)
≥ 2x ULN	and/or	< 20	There are no specific recommendations for dose reductions if present prior to starting azacitidine.
< 2 x ULN	and	< 20	50% on next cycle
≥ 2 X above baseline	and	any	Delay until normal or to baseline; 50% on next cycle

Dosage in the elderly:

No overall differences in safety or effectiveness were observed between younger patients and patients ≥ 65 years. Monitor closely as elderly patients are more likely to have decreased renal function or possibly greater sensitivity to the drug.

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

Azacitidine for injection is **not interchangeable** with, and should not be substituted with or for, azacitidine tablets. Verify drug name, dose, and administration route. The different dosage forms are not bioequivalent.

- For subcutaneous use only. The manufacturer recommends using a fresh 25-gauge subcutaneous needle for injection.
- Follow local guidelines on maximum volumes for subcut injections. The manufacturer recommends that each syringe can contain up to 100mg (4mL) of azacitidine; doses greater than 4 mL should be injected into at least 2 separate sites.
- Discard if the drug contains large particles or agglomerates.
- Do not filter the suspension after reconstitution.
- Before injection, ensure contents of syringe are at room temperature. Contents of the syringe must be re-suspended immediately prior to administration, by vigorously rolling the syringe between the palms until a uniform cloudy suspension is achieved.
- Rotate injection sites; possible sites include the upper arm, thigh or abdomen.
- Do not inject into sites which are red, bruised, tender, or hardened.
- New injections should be given at least 2.5 cm from the previous site.
- If a dose is missed, it should not be given at the same time as the next dose, but should be added to the end of the current dosing cycle.
- Store unopened vials at room temperature (15 to 30°C).

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or any of its components.
- Patients who have advanced malignant hepatic tumours.

Other Warnings/Precautions:

- Use with caution in patients with poor performance status, extensive disease or significant cardiac or lung disease.
- Safety and efficacy have not been established in patients with severe CHF, clinically unstable heart or lung disease.

Pregnancy and Lactation:

- Mutagenicity: Yes
- Clastogenicity: Yes
- Embryotoxicity: Yes

- Teratogenicity: Yes
  Azacitidine is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose.
- Breastfeeding:
  Breastfeeding is not recommended during treatment, and for at least **1 week** after the last dose.
- Fertility effects: Probable

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H - Interactions

No formal clinical drug interactions have been studied with azacitidine. Azacitidine metabolism *in vitro* does not appear to be mediated by CYP450. *In vitro* data also suggest that azacitidine does not induce CYP 450 isoenzymes (CYP 1A2, 2C19, 3A4 or 3A5). CYP450 inhibition (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) at clinically achievable azacitidine plasma concentrations is unlikely.

Canine studies suggest a potential for QTc prolongation; no human studies have been conducted. Use with caution in patients who are taking other medications known to prolong QTc.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, before each cycle and as clinically indicated (to monitor response and toxicity)
Liver function tests	Baseline and before each cycle
Renal function tests	Baseline and before each cycle
Electrolytes and bicarbonate levels	Baseline and before each cycle

Clinical toxicity assessment for differentiation syndrome, bleeding, infection, cardiac, skin/local, neurological, venous thromboembolism, GI and tumour lysis effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

High Cost Therapy Funding Program

- Azacitidine in combination with Venetoclax (Inpatient) - Previously Untreated Acute Myeloid Leukemia

New Drug Funding Program (NDFP Website)

- Azacitidine - Acute Myeloid Leukemia (AML)
- Azacitidine - Intermediate-2 and high-risk myelodysplastic syndrome (MDS)
- Azacitidine - Acute Myeloid Leukemia (AML) Greater Than 30% Blasts
- Azacitidine in combination with Venetoclax (Outpatient) - Previously Untreated Acute Myeloid Leukemia

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K - References

Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A et al. Efficacy of azacitidine compared with conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. Lancet Oncol 2009; 10: 223-32.

Kaminskas E, Farrell AT, Wang YC, et al. FDA Drug Approval Summary: Azacitidine (5-azacytidine, Vidaza™) for Injectable Suspension. The Oncologist 2005; 10: 176-82.

Keating GM. Azacitidine: a review of its use in higher-risk myelodysplastic syndromes/acute myeloid leukaemia. Drugs 2009; 69(17): 2501-18.

NCI Drug Dictionary: Azacitidine. Accessed November 13, 2012

Prescribing Information: Vidaza® (azacitidine). Celgene Corp., September 2022.

Product Monograph: Vidaza® (azacitidine). Celgene Canada, June 20, 2022.

July 2023 Updated indications (to new format), adverse effects, dosing, administration, and monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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