Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

azaCITIDine (tablets)

COMMON TRADE NAME(S): Onureg®

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B - Mechanism of Action and Pharmacokinetics

Azacitidine is a pyrimidine nucleoside analogue of cytidine that when introduced into DNA and RNA, inhibits DNA/RNA methyltransferases, reduces DNA/RNA methylation, alters DNA gene expression (including re-expression of genes that regulate tumor suppression and cell differentiation), and decreases RNA stability and protein synthesis. Incorporation of azacitidine into cancer cells leads to a reduction of cell viability and induction of apoptosis in acute myeloid leukemia (AML) cell lines in vitro. Azacitidine decreased tumor burden and increased survival in leukemic tumor models.

Absorption	Azacitidine exposure was generally linear with dose-proportional increases in systemic exposure; high intersubject variability was observed.	
	Bioavailability	~11% (compared to subcut)
	Effects with food	Co-administration of a high-fat, high-calorie meal delayed Tmax by approximately 1 hour and decreased Cmax by 21%. However, there was no significant impact on AUC.
	Peak plasma levels	1 hour
Distribution	PPB	6-12%

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	Half-life	~ 30 mins
	Urine	<2% as unchanged drug

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C - Indications and Status

Health Canada Approvals:

- 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 – Consider prophylaxis daily (Administer an antiemetic 30 minutes prior to each dose of azacitidine for the first 2 cycles. Administer antiemetic prophylaxis as needed after 2 cycles if there has been no nausea and vomiting.)

The following table lists adverse effects that occurred in ≥ 5% of patients in a phase III study with AML, who had achieved first CR /CRi within 4 months after intensive induction chemotherapy. It also includes severe, life-threatening and post-marketing adverse effects from other sources. Adverse effects marked with "^" were observed post-marketing in intravenous or subcutaneous azacitidine administration.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (2%) (severe)	E
	Cardiotoxicity (rare)^	E

	Venous thromboembolism (rare)^	E
Dermatological	Other - including leukocytoclastic vasculitis, pyoderma gangrenosum, acute febrile neutrophilic dermatosis and necrotizing fasciitis (rare)^	E
Gastrointestinal	Abdominal pain (22%)	E
	Anorexia, weight loss (13%)	E
	Constipation (39%)	E
	Diarrhea (50%) (5% severe)	E
	GI perforation (rare)^	E
	Nausea, vomiting (65%) (3% severe)	E
General	Fall (5%)	E
	Fatigue (44%) (4% severe)	E
Hematological	Myelosuppression ± infection, bleeding (45%) (41% severe; rarely hemorrhagic diathesis^)	E
Hepatobiliary	↑ ALT (5%)	E
	Hepatotoxicity (rare)^	E
	Pancreatitis (rare)^	E
Metabolic / Endocrine	Hyperuricemia (2%) (severe)	E
	Tumor lysis syndrome (rare)^	E
Musculoskeletal	Musculoskeletal pain (14%)	E
Nervous System	Anxiety (7%)	E
	Dizziness (11%)	E
	Seizure (rare)^	E
Renal	Renal failure (rare)^	E
Respiratory	Pneumonitis (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 (tablets) include nausea, vomiting, diarrhea, myelosuppression ± infection, fatigue, constipation, abdominal pain, musculoskeletal pain, anorexia, weight loss and dizziness.

New or worsening ≥ grade 3 **neutropenia** (41%), **thrombocytopenia** (23%), or febrile neutropenia (11%) were commonly reported with azacitidine tablets. The first occurrence of ≥ grade 3 neutropenia, thrombocytopenia, or febrile neutropenia occurred within the first 2 cycles in 20%, 11%, and 2%, respectively.

Progressive hepatic coma has been rarely reported in patients with extensive tumor burden due to metastatic disease when treated with injectable azacitidine, especially in patients with baseline serum albumin < 30 g/L, and may be fatal.

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.

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

At the start of each cycle, initiate azacitidine only when ANC ≥ 0.5 x 10^9/L.

Consider the use of granulocyte colony stimulating factor (GCSF) as clinically indicated.

Consider the use of antidiarrheal medication for prophylaxis against diarrhea and for prompt treatment at the onset of symptoms.

Azacitidine maintenance therapy should be initiated after achievement of a CR/CRi following completion of induction and consolidation therapy or following induction if consolidation therapy is not planned.

Adults:

Oral: 300 mg Daily

on Day 1 through Day 14 every 28 days.

Discontinue if more than 15% blasts are observed in either the peripheral blood or bone marrow or at the physician's discretion.

Dosage with Toxicity:

Dose Level	Azacitidine Dose (mg/day)
0	300
-1	200

Toxicity	Criteria	Occurrence	Action
Neutropenia	ANC < 0.5 x 10^9/L OR ANC < 0.5-1 x 10^9/L with fever	First	Hold; consider use of GCSF as clinically indicated. Resume at same dose after recovery to ≤ grade 2.
		2 Consecutive Cycles	Hold; consider use of GCSF as clinically indicated. Resume at ↓ 1 dose level after recovery to ≤ grade 2.
		Continued or recurrent toxicity after dose reduction	Reduce treatment duration to 7 days (e.g. treat on days 1-7 instead of days 1-14 every 28 days). Consider use of GCSF as clinically indicated.
		Continued toxicity or recurrence after dose and schedule reduction	Discontinue.

Thrombocytopenia	Platelets < 25 x 10^9/L OR Platelets < 25-50 x 10^9/L with bleeding	First	Hold; resume at same dose after recovery to ≤ grade 2.
		2 Consecutive Cycles	Hold; resume at ↓ 1 dose level after recovery to ≤ grade 2.
		Continued or recurrent toxicity after dose reduction	Reduce treatment duration to 7 days (e.g. treat on days 1-7 instead of days 1-14 every 28 days).
		Continued toxicity or recurrence after dose and schedule reduction	Discontinue.
Nausea, Vomiting or Diarrhea	≥ Grade 3	First	Hold; resume at same dose after recovery to ≤ grade 1.
		Second	Hold; resume at ↓ 1 dose level after recovery to ≤ grade 1.
		Continued or recurrent toxicity after dose reduction	Reduce treatment duration to 7 days (e.g. treat on days 1-7 instead of days 1-14 every 28 days).
		Continued toxicity or recurrence after dose and schedule reduction	Discontinue.
All other nonhematologic toxicities	≥ Grade 3	First	Hold and provide medical support; resume at same dose after recovery to ≤ grade 1.
		Second	Hold; resume at ↓ 1 dose level after recovery to ≤ grade 1.
		Continued or recurrent toxicity after dose reduction	Reduce treatment duration to 7 days (e.g. treat on days 1-7 instead of days 1-14 every 28 days).
		Continued toxicity or recurrence after dose and schedule reduction	Discontinue.

Dosage with Hepatic Impairment:

Hepatic Impairment	Azacitidine Dose (mg/day)
Mild impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 1.5 x ULN and any AST)	No dose adjustment is required
Moderate impairment (total bilirubin >1.5 to 3 x ULN)	Dose adjustment has not been established
Severe impairment (total bilirubin >3 x ULN)	Has not been studied

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Azacitidine Dose (mg/day)
≥30	No dose adjustment is required
<30	No initial dose adjustment required; monitor patients more frequently and modify dosage for adverse reactions

Dosage in the elderly:

No dose adjustment is required. No overall differences in safety or effectiveness were observed between younger patients and patients ≥ 65 years.

Children:

The safety and effectiveness of azacitidine in pediatric patients have not been established.

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F - Administration Guidelines

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

- Take with or without food at approximately the same time each day.
- Swallow tablets whole with water. Do not split, crush or chew the tablets.
- If a dose of azacitidine is missed, administer the dose as soon as possible on the same day, and return to the normal time of dose administration the following day. Do not take 2 doses on the same day.
- If a dose is vomited, do not take another dose on the same day, return to the normal time of dose administration the following day.
- Store blisters at 15º to 30ºC. Store in the original aluminum blisters.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to the drug or any component of the formulation.
- Patients with advanced malignant hepatic tumors.

Other Warnings/Precautions:

- **DO NOT** substitute azacitidine tablets for intravenous or subcutaneous azacitidine. There are substantial differences in the pharmacokinetic parameters. The recommended dose and schedule of azacitidine tablets are different from those of the intravenous or subcutaneous azacitidine products.Treatment of patients using intravenous or subcutaneous azacitidine at the recommended dosage of azacitidine tablets may result in a fatal adverse reaction. Treatment of patients using azacitidine tablets at the doses recommended for intravenous or subcutaneous azacitidine may not be effective.
- The safety and effectiveness of azacitidine tablets for treatment of myelodysplastic syndromes have not been established. A higher incidence of early fatal and/or serious adverse reactions was observed in clinical trials. Treatment of patients with myelodysplastic syndromes is not recommended outside of controlled trials.

- The safety and efficacy of azacitidine tablets in patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease have not been established as they were excluded from the pivotal clinical study.
- No thorough clinical QT/QTc study or in vitro studies were performed to rule out the effect of azacitidine tablets on QT prolongation. An *in vivo* safety pharmacology animal study reported increased QTc interval, but interpretation of the study is limited by confounding effects associated with toxicity.
- Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Patients should be advised that they may experience effects such as fatigue and asthenia and caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Clastogenicity: Yes
- Mutagenicity: Yes
- Fetotoxicity: Yes
- Embryotoxicity: Yes
  Azacitidine tablets are 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.
- Excretion into breast milk:
  Breastfeeding is not recommended during treatment and for **1 week** after the last dose.
- Fertility effects:
  Observed in animal studies

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H - Interactions

- Interactions with CYP inhibitors and inducers are unlikely to have any impact on the metabolism of azacitidine as its metabolism does not appear to be mediated by CYP450 isoforms.
- CYP induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.
- Azacitidine does not inhibit and is not a substrate of P-glycoprotein (P-gp).
- Azacitidine uptake is unlikely to be altered by single nucleotide polymorphisms in individual nucleoside transporters or nucleoside modulators.
- A dose modification is not required when azacitidine is coadministered with proton pump inhibitors or other pH modifiers.
- In vitro, azacitidine did not inhibit breast cancer resistance protein (BCRP), organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptides (OATP) OATP1B1 and OATP1B3, or organic cation transporter (OCT) OCT2.

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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	Every other week for the first 2 cycles (56 days), every other week for the next 2 cycles after any dose adjustment, then monthly before each cycle and as clinically indicated
Renal function tests	Baseline, before each cycle and as clinically indicated, more frequently in patients with severe renal impairment (ClCr <30 mL/min)

Liver function tests	Baseline, before each cycle and as clinically indicated
Clinical toxicity assessment for infection, bleeding, fatigue, hyperuricemia, falls, and cardiovascular and gastrointestinal effects	Baseline and as clinically indicated

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

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- azaCITIDine (tablets) - For maintenance therapy in adult patients with AML who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment, and who are not eligible for hematopoietic stem cell transplantation

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K - References

Prescribing Information: Onureg (azacitidine) tablets . Summit, NJ: Celgene Inc., a Bristol-Myers Squibb company, March 2021.

Product Monograph: Onureg (azacitidine tablets). Saint-Laurent, QC: Celgene Inc., a Bristol-Myers Squibb company, January 2021.

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

Wei AH, Dohner H, Pocock C, et al. Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission. N Engl J Med 2020;383:2526-37.
DOI: 10.1056/NEJMoa2004444

July 2023 Updated adverse effects section

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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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