DRUG NAME: Azacitidine

SYNONYM(S): ladakamycin[1]

COMMON TRADE NAME(S): VIDAZA®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Azacitidine is a synthetic pyrimidine nucleoside analog of cytidine. Azacitidine appears to exert its antineoplastic effect by multiple mechanisms, including a direct cytotoxic effect on abnormal hematopoietic cells in the bone marrow through incorporation into DNA and RNA, and an inhibition of DNA methyltransferase, causing hypomethylation of DNA. Hypomethylation may restore normal function to genes critical for differentiation and proliferation. Nonproliferating cells are relatively insensitive to azacitidine.[1,2] The relative importance of DNA hypomethylation versus cytotoxicity mechanism has not been established.[2]

PHARMACOKINETICS:

Absorption	rapid following subcutaneous injection (89% bioavailability relative to IV)	
Distribution	peak plasma concentrations occurring at 0.5 h	
	cross blood brain barrier?	no[3]
	volume of distribution	76 ± 26 L (IV); not calculated for SC
	plasma protein binding	no information found
Metabolism	by spontaneous hydrolysis (primarily) and deamination by cytidine deaminase; several metabolites (unnamed)[3]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily in urine for parent compound and metabolites	
	urine	50-85%
	feces	<1%
	terminal half life	41 ± 8 min (SC); 22 ± 1 min (IV)
	clearance	167 ± 49 L/h (SC); 147 ± 47 L/h (IV)
Elderly	no overall difference in safety and effectiveness	

Adapted from standard reference[4] unless specified otherwise.

USES:

Primary uses:

*Myelodysplastic syndromes

*Leukemia, acute myeloid

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- advanced malignant hepatic tumours[2]

Caution:
- the oral formulation of azacitidine is ***NOT interchangeable*** with the injectable formulation and should not be substituted.[5]
- ***tumour lysis syndrome*** has been reported; patients with high tumour burden prior to treatment are at risk[4]

Carcinogenicity: In animal studies, azacitidine has shown carcinogenic potential, inducing tumours of the hematopoietic system, and increasing the incidence of tumours in the lymphoreticular system, lung, mammary gland, skin, and testes.[2]

Mutagenicity: Mutagenic in Ames test and other *in vitro* bacterial microsome tests. Azacitidine is clastogenic in mammalian *in vitro* chromosome tests.[4]

Fertility: In animal studies, azacitidine has produced adverse effects on male reproduction and fertility (i.e., decreased testes and epididymides weights as well as decreased sperm count) and decreased pregnancy rates.[4] At some doses, treated males were fertile, but when mated with untreated females, there was an increase in preimplantation embryo loss and/or the average number of abnormal embryos was increased.[5]

Pregnancy: In animal studies, azacitidine was teratogenic and caused embryo-fetal lethality at doses less than the recommended human daily dose. Findings included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, oedema, and rib abnormalities). Women of childbearing potential and male patients with female sexual partners of childbearing potential should use effective contraception during treatment and for six months following treatment.[5]

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[6,7]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia (see paragraph following **Side Effects** table)	***anemia*** (51-70%, severe 14%); mean time to nadir is 15-16 days[8]
	febrile neutropenia (14-16%, severe 13%)
	leukopenia (18-48%, severe 15%)
	neutropenia (32-66%, severe 61%); mean time to nadir is 15-16 days[8]
	pancytopenia (<10%)[4]
	thrombocytopenia (66-70%; severe 58%); mean time to nadir is 15-16 days[8]
cardiac	atrial fibrillation (<1%)
	congestive heart failure (<1%)
	pericardial effusion (<1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
eye	conjunctival hemorrhage (1-10%)
gastrointestinal	*emetogenic potential:* moderate[9]
	abdominal pain, tenderness (12-13%, severe 4%)
	colitis (<1%)
	constipation (34-50%, severe 1%); possibly more pronounced in cycles 1-2; incidence may increase with higher doses
	diarrhea (6-36%); incidence may increase with higher doses
	dyspepsia (6%)
	gastrointestinal hemorrhage (<10%)[4]
	gingival bleeding (10%)
	hemorrhoidal hemorrhage (<10%)[4]
	mouth hemorrhage (5%)
	nausea (48-71%, severe 2%); possibly more pronounced in cycles 1-2; incidence may increase with higher doses
	pancreatitis (<1%)
	stomatitis (8%)
	vomiting (27-54%, severe 0%); possibly more pronounced in cycles 1-2; incidence may increase with higher doses
general disorders and administration site conditions	*extravasation hazard:* irritant[10]
	fatigue (24%, severe 3%)
	injection site bruising (5-14%), ***erythema*** (35-43%) and ***pain*** (19-23%); possibly more pronounced in cycles 1-2; incidence may increase with higher doses
	injection site necrosis[4] (<1%)
	injection site reactions: hematoma (6%); induration, granuloma (10%); pigmentation changes (5%), pruritus (7%), swelling (5%), and rash (5%)
	malaise (11%)
	peripheral edema (<1%)
	pyrexia (30-52%, severe 5%)
hepatobiliary	ascites (<1%)
	hepatitis, hepatic failure (<1%)
	jaundice (<1%)
immune system	hypersensitivity reaction (<1%)
infections and infestations	neutropenic sepsis (<2%)
	pneumonia (4-11%)
	rhinitis (6%)
	upper respiratory tract infection (9-15%, severe 2%)
	urinary tract infection (9%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
injury, poisoning, and procedural complications	post procedural hemorrhage (6%)
investigations	AST, ALT elevation[4] (<1%)
	blood creatinine elevation[4] (<1%)
	hyperbilirubinemia (<1%)
	weight decrease (8%, severe 1%)
metabolism and nutrition	***anorexia*** (21%)
	dehydration[4] (<1%)
	hyperglycemia[4] (<1%)
	hypokalemia (6%, severe 2%); possibly more pronounced in cycles 1-2
	hyponatremia[4] (<1%)
	tumour lysis syndrome[4] (<1%)
musculoskeletal and connective tissue	***arthralgias, myalgias*** (16-22%)
	chest pain, chest wall pain (5-16%)
nervous system	cerebral hemorrhage (2%)
	convulsion[4] (<1%)
	dizziness (19%); possibly more pronounced in cycles 1-2
	headache (22%)
	lethargy (7-8%)
psychiatric	anxiety (5-13%); possibly more pronounced in cycles 1-2
	confusion (1-10%)
	insomnia (9-11%); possibly more pronounced in cycles 1-2
renal and urinary	hematuria (6%, severe 2%)
	renal failure[4] (<1%); see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	***dyspnea*** (15-30%, severe 3%)
	dyspnea, exertional (5%)
	interstitial lung disease[4] (<1%)
	pharyngolaryngeal pain (6%)
	pulmonary embolism[4] (<1%)
	respiratory distress syndrome[4] (<1%)
skin and subcutaneous tissue	alopecia (<10%)[4]
	dry skin (5%)
	erythema (7-17%)
	leukocytoclastic vasculitis[4] (<1%)
	petechiae, ecchymosis (11-31%, severe 1%); possibly more pronounced in cycles 1-2

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pruritus (12%)
	rash (10-14%)
	Sweet's syndrome[4] (<1%)
	urticaria (6%)
vascular	hematoma (9%)
	hypertension (9%, severe 1%)
	hypotension (7%)

Adapted from standard reference[2] unless specified otherwise.

Hematologic toxicity (i.e., anemia, neutropenia, leukopenia, and thrombocytopenia) is associated with azacitidine therapy, particularly during the first two cycles and less frequently thereafter.[4,11] Incidence also tends to increase with higher doses.[4] Mean time to nadir is 15-16 days in all cycles.[8] Consider treatment delay or dose reduction for hematologic toxicity depending on nadir values and length of time until recovery.[4]

Following ***oral administration*** of azacitidine, hematologic and gastrointestinal events are the most common adverse events reported. Discontinuation of oral azacitidine for adverse events is infrequent. Hematologic events are relatively common, with neutropenia, thrombocytopenia, and anemia reported. Events are generally manageable with temporary treatment delays and/or dose reductions. Prophylaxis for neutropenia may be required. GI events are usually low-grade and the frequency appears to decrease after the initial cycles, suggesting a progressive GI tolerance to oral azacitidine. Prophylactic antiemetics may be beneficial during the first 2 treatment cycles to facilitate treatment compliance.[12] Diarrhea should be promptly managed with antidiarrheal medications at the onset of symptoms.[5]

Renal abnormalities ranging from elevated serum creatinine to renal failure and death have been reported with intravenous azacitidine in combination with other chemotherapy. Severe renal tubular dysfunction may manifest as hypophosphatemia, hypokalemia, or hyponatremia, with or without increases in serum creatinine and blood urea nitrogen (BUN). Renal tubular acidosis (serum bicarbonate <20 mmol/L, serum potassium <3 mmol/L, and alkaline urine), although rare, has also been reported. Monitor serum electrolytes, bicarbonate, creatinine, and BUN during treatment. Consider dose reduction or treatment delays for unexplained reductions in serum bicarbonate or elevations in serum creatinine or BUN during treatment as suggested below:

- for serum bicarbonate <20 mmol/L: consider 50% dose reduction for next cycle;
- for serum creatinine or BUN ≥ 2 fold above baseline or ULN: consider treatment delay until values return to normal or baseline, then 50% dose reduction for next cycle.

Monitor for increased toxicity in patients with renal impairment as azacitidine and its metabolites are primarily excreted through the kidney.[4]

INTERACTIONS: No information found; it is considered unlikely that azacitidine will have clinically significant inhibitory or inductive effects on cytochrome P450 enzymes or be affected by CYP inhibitors or inducers.[2]

SUPPLY AND STORAGE:

Oral: Celgene Inc. supplies azacitidine as 200 mg and 300 mg tablets. Tablets contain lactose. Store at room temperature in original aluminum blisters.[5]

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Additional information:
- tablets are supplied in 7 count blister packages[5]
- do not crush tablets; if powder comes into contact with skin or mucous membranes, immediately wash with soap and/or flush with water[5]

***Injection*:** Celgene Inc. supplies azacitidine as a sterile lyophilized powder for reconstitution in 100 mg single-use vials. Store at room temperature.[4]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- D5W, hetastarch in sodium chloride (HESPAN®), or solutions containing bicarbonate have the potential to increase the rate of degradation of azacitidine.[4]
- preparations intended for subcutaneous administration cannot be given by other routes; unique reconstitution and dilution instructions apply to preparations intended for routes other than subcutaneous administration.[13]
- stability of azacitidine is highly temperature sensitive; reconstituted azacitidine degrades more slowly at cold temperatures[14,15]; stability may be extended by using a cold diluent for reconstitution or by refrigerating or freezing the reconstituted solution.[15-20]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	• ***into the upper arm, thigh, or abdomen; rotate sites of injection*** [4] • volumes up to and including 4 mL may be injected into a single site; ***volumes greater than 4 mL*** are to be injected into ***two separate sites***[4,21] • using the ***"air sandwich"*** technique for subcutaneous administration may reduce the risk and severity of injection site reactions[22]
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	has been used[13,23,24]
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

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DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Oral:	***4 weeks***[5,25,26]:	***300 mg*** (range 200-300 mg***) PO once daily for 14 consecutive days starting on day 1*** (total dose per cycle 4200 mg [range 2800-4200 mg]) Administer with food or on an empty stomach.
Subcutaneous:	***4 weeks***:[4,27,28]	***75 mg/m²*** (range 37.5-100 mg/m^2) ***SC once daily for 7 consecutive days starting on day 1*** (total dose per cycle 525 mg/m^2 [range 262.5 -700 mg/m^2]) If a dose is missed during the 7 days of treatment, it should be added to the end of the current dosing cycle.
	4 weeks:[11,27,28]	If treatment must be interrupted by weekends, alternative dosing schedules that eliminate weekend dosing have been used: ***75 mg/m² SC*** (range 37.5-75 mg/m^2) ***once daily for 5 consecutive days starting on day 1, no treatment on days 6-7, then 75 mg/m² SC once daily for 2 consecutive days starting on day 8*** (for a total of 7 days of treatment per cycle given 5 on -2 off -2 on) (total dose per cycle 525 mg/m^2 [range 262.5 -525 mg/m^2]) OR 50 mg/m^2 SC once daily for 5 consecutive days starting on day 1, no treatment on days 6-7, then 50 mg/m^2 SC once daily for 5 consecutive days starting on day 8 (for a total of 10 days of treatment given 5 on -2 off -5 on) (total dose per cycle 500 mg/m^2) OR 75 mg/m^2 SC once daily for 5 consecutive days starting on day 1 (total dose per cycle 375 mg/m^2) The efficacy of alternate dosing schedules is not known.[11]
Concurrent radiation:	no information found	

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Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
Dosage in renal failure:	mild to severe impairment: no dose adjustment required; monitor for toxicity, particularly in patients with creatinine clearance ≤29 mL/min[5,29]
Dosage in hepatic failure:	***oral*** administration: • mild impairment: no dose adjustment required[5] • moderate to severe impairment: no information found ***subcutaneous*** administration: • no information found
Dosage in dialysis:	no information found

Children: has been used[27]

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