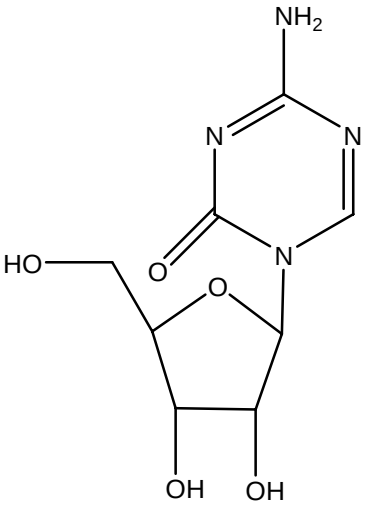
VIDAZA®
(azacitidine for injection) R_x only

For subcutaneous and intravenous use only

DESCRIPTION

VIDAZA® (azacitidine for injection) contains azacitidine, which is a pyrimidine nucleoside analog of cytidine. Azacitidine is 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one. The structural formula is as follows:



The empirical formula is $C_8H_{12}N_4O_5$. The molecular weight is 244. Azacitidine is a white to off-white solid. Azacitidine was found to be insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water-saturated octanol, 5% dextrose in water, N-methyl-2-pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

The finished product is supplied in a sterile form for reconstitution as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion. Vials of VIDAZA contain 100 mg of azacitidine and 100 mg of mannitol as a sterile lyophilized powder.

CLINICAL PHARMACOLOGY

Mechanism of Action

VIDAZA is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death

of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms. Nonproliferating cells are relatively insensitive to VIDAZA.

Pharmacokinetics

The pharmacokinetics of azacitidine were studied in 6 MDS patients following a single 75 mg/m^2 subcutaneous (SC) dose and a single 75 mg/m^2 intravenous (IV) dose. Azacitidine is rapidly absorbed after SC administration; the peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in 0.5 hour. The bioavailability of SC azacitidine relative to IV azacitidine is approximately 89%, based on area under the curve. Mean volume of distribution following IV dosing is 76 ± 26 L. Mean apparent SC clearance is 167 ± 49 L/hour and mean half-life after SC administration is 41 ± 8 minutes.

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following IV administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion accounted for <1% of administered radioactivity over 3 days. Mean excretion of radioactivity in urine following SC administration of ^{14}C-azacitidine was 50%. The mean elimination half-lives of total radioactivity (azacitidine and its metabolites) were similar after IV and SC administrations, about 4 hours.

Special Populations

The effects of renal or hepatic impairment, gender, age, or race on the pharmacokinetics of azacitidine have not been studied. (See **CONTRAINDICATIONS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION.**)

Drug-Drug Interactions

Drug interaction studies with azacitidine have not been conducted.

An in vitro study of azacitidine incubation in human liver fractions indicated that azacitidine may be metabolized by the liver. Whether azacitidine metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied.

The potential of azacitidine to inhibit cytochrome P450 (CYP) enzymes is not known.

In vitro studies with human cultured hepatocytes indicate that azacitidine at concentrations of 1.0 μM to 100 μM does not induce CYP 1A2, 2C19, or 3A4/5.

CLINICAL STUDIES

A randomized, open-label, controlled trial carried out in 53 U.S. sites compared the safety and efficacy of subcutaneous VIDAZA plus supportive care with supportive care alone ("observation") in patients with any of the 5 FAB subtypes of myelodysplastic syndromes (MDS): refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts

(RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL). RA and RARS patients were included if they met one or more of the following criteria: required packed RBC transfusions; had platelet counts ≤ 50.0 x 10^9/L; required platelet transfusions; or were neutropenic (ANC < 1.0 x 10^9/L) with infections requiring treatment with antibiotics. Patients with acute myelogenous leukemia (AML) were not intended to be included. Baseline patient and disease characteristics are summarized in Table 1; the 2 groups were similar.

VIDAZA was administered at a subcutaneous dose of 75 mg/m^2 daily for 7 days every 4 weeks. The dose was increased to 100 mg/m^2 if no beneficial effect was seen after 2 treatment cycles. The dose was decreased and/or delayed based on hematologic response or evidence of renal toxicity. Patients in the observation arm were allowed by protocol to cross over to VIDAZA if they had increases in bone marrow blasts, decreases in hemoglobin, increases in red cell transfusion requirements, or decreases in platelets, or if they required a platelet transfusion or developed a clinical infection requiring treatment with antibiotics. For purposes of assessing efficacy, the primary endpoint was response rate (as defined in Table 2).

Of the 191 patients included in the study, independent review (adjudicated diagnosis) found that 19 had the diagnosis of AML at baseline. These patients were excluded from the primary analysis of response rate, although they were included in an intent-to-treat (ITT) analysis of all patients randomized. Approximately 55% of the patients randomized to observation crossed over to receive VIDAZA treatment.

Table 1. Baseline Demographics and Disease Characteristics

	VIDAZA (N=99)	Observation (N=92)
Gender (n%)		
Male	72 (72.7)	60 (65.2)
Female	27 (27.3)	32 (34.8)
Race (n%)		
White	93 (93.9)	85 (92.4)
Black	1 (1.0)	1 (1.1)
Hispanic	3 (3.0)	5 (5.4)
Asian/Oriental	2 (2.0)	1 (1.1)
Age (years)		
N	99	91
Mean ± SD	67.3 ± 10.39	68.0 ± 10.23
Range	31–92	35–88
Adjudicated MDS diagnosis at study entry (n%)		
RA	21 (21.2)	18 (19.6)
RARS	6 (6.1)	5 (5.4)
RAEB	38 (38.4)	39 (42.4)
RAEB-T	16 (16.2)	14 (15.2)
CMMoL	8 (8.1)	7 (7.6)
AML	10 (10.1)	9 (9.8)
Transfusion product used in 3 months before study entry (n%)		
Any transfusion product	70 (70.7)	59 (64.1)
Blood cells, packed human	66 (66.7)	55 (59.8)
Platelets, human blood	15 (15.2)	12 (13.0)
Hetastarch	0(0.0)	1(1.1)
Plasma protein fraction	1(1.0)	0(0.0)
Other	2(2.0)	2(2.2)

Table 2. Response Criteria

		RA	RARS	RAEB	RAEB-T	CMMoL
Complete Response (CR), duration ≥ 4 weeks	**Marrow**	< 5% blasts				
	Peripheral Blood	Normal CBC if abnormal at baseline Absence of blasts in the peripheral circulation				
Partial Response (PR), duration ≥ 4 weeks	**Marrow**	No marrow requirements		≥ 50% decrease in blasts Improvement of marrow dyspoiesis		
	Peripheral Blood	≥ 50% restoration in the deficit from normal levels of baseline white cells, hemoglobin, and platelets if abnormal at baseline No blasts in the peripheral circulation For CMMoL, if WBC is elevated at baseline, a ≥ 75% reduction in the excess count over the upper limit of normal				

The overall response rate (CR + PR) of 15.7% in VIDAZA-treated patients without AML (16.2% for all VIDAZA randomized patients including AML) was statistically significantly higher than the response rate of 0% in the observation group ($p<0.0001$) (Table 3). The majority of patients who achieved either CR or PR had either 2 or 3 cell line abnormalities at baseline (79%; 11/14) and had elevated bone marrow blasts or were transfusion dependent at baseline. Patients responding to VIDAZA had a decrease in bone marrow blasts percentage, or an increase in platelets, hemoglobin or WBC. Greater than 90% of the responders initially demonstrated these changes by the 5th treatment cycle. All patients who had been transfusion dependent became transfusion independent during PR or CR. The mean and median duration of clinical response of PR or better was estimated as 512 and 330 days, respectively; 75% of the responding patients were still in PR or better at completion of treatment. Response occurred in all MDS subtypes as well as in patients with adjudicated baseline diagnosis of AML.

Table 3. Response Rates

	VIDAZA (N=89)	Observation Before Crossover (N=83)	
Response	**n (%)**	**N (%)**	**P value**
Overall (CR+PR)	14 (15.7)	0 (0.0)	(<0.0001)
Complete (CR)	5 (5.6)	0 (0.0)	(0.06)
Partial (PR)	9 (10.1)	0 (0.0)	--

Patients in the observation group who crossed over to receive VIDAZA treatment (47 patients) had a response rate of 12.8%.

A multi-center, open-label, single-arm study of 72 patients with RAEB, RAEB-T, CMMoL, or AML was also carried out. Treatment with subcutaneous VIDAZA resulted in a response rate (CR + PR) of 13.9%, using criteria similar to those described above. The mean and median duration of clinical response of PR or better was estimated as 810 and 430 days, respectively; 80% of the responding patients were still in PR or better at the time of completion of study involvement. In another open-label, single-arm study of 48 patients with RAEB, RAEB-T, or AML, treatment with intravenous VIDAZA resulted in a response rate of 18.8%, again using criteria similar to those described above. The mean and median duration of clinical response of PR or better was estimated as 389 and 281 days, respectively; 67% of the responding patients were still in PR or better at the time of completion of treatment. Response occurred in all MDS subtypes as well as in patients with adjudicated baseline diagnosis of AML in both of these studies. VIDAZA dosage regimens in these 2 studies were similar to the regimen used in the controlled study.

Benefit was seen in patients who did not meet the criteria for PR or better, but were considered "improved." About 24% of VIDAZA-treated patients were considered improved, and about 2/3 of those lost transfusion dependence. In the observation group, only 5/83 patients met criteria for improvement; none lost transfusion dependence. In all 3 studies, about 19% of patients met criteria for improvement, with a median duration of 195 days.

Response rate estimates were similar regardless of age or gender.

INDICATIONS AND USAGE

VIDAZA is indicated for treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.

CONTRAINDICATIONS

VIDAZA is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol. VIDAZA is also contraindicated in patients with advanced malignant hepatic tumors. (See **PRECAUTIONS.**)

WARNINGS

Pregnancy—Teratogenic Effects: Pregnancy Category D

VIDAZA may cause fetal harm when administered to a pregnant woman. Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single IP (intraperitoneal) injection of 6 mg/m^2 (approximately 8% of the recommended human daily dose on a mg/m^2 basis) azacitidine on gestation day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation day 15 at doses of ~3–12 mg/m^2 (approximately 4%–16% the recommended human daily dose on a mg/m^2 basis).

In rats, azacitidine was clearly embryotoxic when given IP on gestation days 4–8 (postimplantation) at a dose of 6 mg/m^2 (approximately 8% of the recommended human daily dose on a mg/m^2 basis), although treatment in the preimplantation period (on gestation days 1–3) had no adverse effect on the embryos. Azacitidine caused multiple fetal abnormalities in rats after a single IP dose of 3–12 mg/m^2 (approximately 8% the recommended human daily dose on a mg/m^2 basis) given on gestation day 9, 10, 11, or 12. In this study azacitidine caused fetal death when administered at 3–12 mg/m^2 on gestation days 9 and 10; average live animals per litter was reduced to 9% of control at the highest dose on gestation day 9. Fetal anomalies included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, clubfoot, syndactyly, oligodactyly), and others (micrognathia, gastroschisis, edema, and rib abnormalities).

There are no adequate and well-controlled studies in pregnant women using VIDAZA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with VIDAZA.

Use in Males

Men should be advised to not father a child while receiving treatment with VIDAZA. (See **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility** for discussion of premating effects of azacitidine exposure on male fertility and embryonic viability.)

PRECAUTIONS

General

Treatment with VIDAZA is associated with neutropenia and thrombocytopenia. Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be reduced or delayed based on nadir counts and hematologic response as described in **DOSAGE AND ADMINISTRATION**.

Safety and effectiveness of VIDAZA in patients with MDS and hepatic or renal impairment have not been studied as these patients were excluded from the clinical trials.

Because azacitidine is potentially hepatotoxic in patients with severe preexisting hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been rarely reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors. (See **CONTRAINDICATIONS.**)

Renal abnormalities ranging from elevated serum creatinine to renal failure and death have been reported rarely in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents for nonMDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L) developed in 5 patients with CML treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate <20 mEq/L or elevations of BUN or serum creatinine occur, the dosage should be reduced or held as described in **DOSAGE AND ADMINISTRATION.**

Patients with renal impairment should be closely monitored for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys. (See **DOSAGE AND ADMINISTRATION** section.)

Information for Patients

Patients should inform their physician about any underlying liver or renal disease.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with VIDAZA.

Men should be advised to not father a child while receiving treatment with VIDAZA.

Laboratory Tests

Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each cycle. Liver chemistries and serum creatinine should be obtained prior to initiation of therapy.

Drug Interactions

No formal assessments of drug-drug interactions between VIDAZA and other agents have been conducted. (See **CLINICAL PHARMACOLOGY**.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumors of the hematopoietic system in female mice at 2.2 mg/kg (6.6 mg/m^2, approximately 8% the recommended human daily dose on a mg/m^2 basis) administered IP 3 times per week for 52 weeks. An increased incidence of tumors in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine IP at 2.0 mg/kg (6.0 mg/m^2, approximately 8% the recommended human daily dose on a mg/m^2 basis) once a week for 50 weeks. A tumorigenicity study in rats dosed twice weekly at 15 or 60 mg/m^2 (approximately 20%–80% the recommended human daily dose on a mg/m^2 basis) revealed an increased incidence of testicular tumors compared with controls.

The mutagenic and clastogenic potential of azacitidine was tested in *in vitro* bacterial systems Salmonella typhimurium strains TA100 and several strains of trpE8, Escherichia coli strains WP14 Pro, WP3103P, WP3104P, and CC103; in *in vitro* forward gene mutation assay in mouse lymphoma cells and human lymphoblast cells; and in an *in vitro* micronucleus assay in mouse L5178Y lymphoma cells and Syrian hamster embryo cells. Azacitidine was mutagenic in bacterial and mammalian cell systems. The clastogenic effect of azacitidine was shown by the induction of micronuclei in L5178Y mouse cells and Syrian hamster embryo cells.

Administration of azacitidine to male mice at 9.9 mg/m^2 (approximately 9% the recommended human daily dose on a mg/m^2 basis) daily for 3 days prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats 3 times per week for 11 or 16 weeks at doses of 15–30 mg/m^2 (approximately 20%–40%, the recommended human daily dose on a mg/m^2 basis) resulted in decreased weight of the testes and epididymides, and decreased sperm counts accompanied by decreased pregnancy rates and increased loss of embryos in mated females. In a related study, male rats treated for 16 weeks at 24 mg/m^2 resulted in an increase in abnormal embryos in mated females when examined on day 2 of gestation. (See **WARNINGS**.)

Pregnancy

Teratogenic Effects: Pregnancy Category D. (See **WARNINGS**.)

Nursing Mothers

It is not known whether azacitidine or its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for azacitidine in animal studies and the potential for serious adverse reactions, women treated with azacitidine should not nurse.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of patients in the 3 clinical studies described in **CLINICAL STUDIES**, above, 62% were 65 years and older and 21% were 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. In addition there were no relevant differences in the frequency of adverse events observed in patients 65 years and older compared to younger patients.

Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. (See **DOSAGE AND ADMINISTRATION** section.)

ADVERSE REACTIONS

Overview

Adverse Reactions Described in Other Labeling Sections: neutropenia, thrombocytopenia, elevated serum creatinine, renal failure, renal tubular acidosis, hypokalemia, hepatic coma.

Most Commonly Occurring Adverse Reactions (SC or IV Route): nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, fatigue, injection site erythema, constipation, neutropenia, ecchymosis. The most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia.

Adverse Reactions Most Frequently (>2%) Resulting in Clinical Intervention (SC or IV Route):
Discontinuation: leukopenia (5.0%), thrombocytopenia (3.6%), neutropenia (2.7%).
Dose Held: leukopenia (4.5%), neutropenia (4.5%), febrile neutropenia (2.7%).
Dose Reduced: leukopenia (4.5%), neutropenia (4.1%), thrombocytopenia (3.2%).

Discussion of Adverse Reactions Information

The data described below reflect exposure to VIDAZA in 268 patients, including 116 exposed for 6 cycles (approximately 6 months) or more and 60 exposed for greater than 12 cycles (approximately 1 year). VIDAZA was studied primarily in supportive-care–controlled and uncontrolled trials (n = 150 and n = 118, respectively). The population in the subcutaneous studies (n = 220) was 23 to 92 years old (mean 66.4 years), 68% male, and 94% white, and had MDS or AML. The population in the IV study (n = 48) was 35 to 81 years old (mean 63.1 years), 65% male, and 100% white. Most patients received average daily doses between 50 and 100 mg/m^2.

The following table presents the most common adverse events, whether or not considered drug related by investigators, occurring in at least 5% of patients treated with VIDAZA in the supportive-care–controlled trial and the uncontrolled subcutaneous trial combined. It is important to note that duration of exposure was longer for the VIDAZA-treated group than for the observation group: patients received VIDAZA for a mean of 11.4 months while mean time in the observation arm was 6.1 months.

Table 4: Most Frequently Observed Adverse Events (≥ 5% in All VIDAZA)[a]

Preferred Term[b]	All VIDAZA[c] (N=220)	Observation[d] (N=92)
At least 1 TEAE	219 (99.5)	89 (96.7)
Nausea	155 (70.5)	16 (17.4)
Anemia	153 (69.5)	59 (64.1)
Thrombocytopenia	144 (65.5)	42 (45.7)
Vomiting	119 (54.1)	5 (5.4)
Pyrexia	114 (51.8)	28 (30.4)
Leukopenia	106 (48.2)	27 (29.3)
Diarrhea	80 (36.4)	13 (14.1)
Fatigue	79 (35.9)	23 (25.0)
Injection site erythema	77 (35.0)	0
Constipation	74 (33.6)	6 (6.5)
Neutropenia	71 (32.3)	10 (10.9)
Ecchymosis	67 (30.5)	14 (15.2)
Cough	65 (29.5)	14 (15.2)
Dyspnea	64 (29.1)	11 (12.0)
Weakness	64 (29.1)	19 (20.7)
Rigors	56 (25.5)	10 (10.9)
Petechiae	52 (23.6)	8 (8.7)
Injection site pain	50 (22.7)	0
Arthralgia	49 (22.3)	3 (3.3)
Headache	48 (21.8)	10 (10.9)
Anorexia	45 (20.5)	6 (6.5)
Pain in limb	44 (20.0)	5 (5.4)
Pharyngitis	44 (20.0)	7 (7.6)
Back pain	41 (18.6)	7 (7.6)
Contusion	41 (18.6)	9 (9.8)

Preferred Term[b]	All VIDAZA[c] (N=220)	Observation[d] (N=92)
At least 1 TEAE	219 (99.5)	89 (96.7)
Dizziness	41 (18.6)	5 (5.4)
Edema peripheral	41 (18.6)	10 (10.9)
Erythema	37 (16.8)	4 (4.3)
Chest pain	36 (16.4)	5 (5.4)
Epistaxis	36 (16.4)	9 (9.8)
Febrile neutropenia	36 (16.4)	4 (4.3)
Myalgia	35 (15.9)	2 (2.2)
Weight decreased	35 (15.9)	10 (10.9)
Abdominal pain	34 (15.5)	12 (13.0)
Pallor	34 (15.5)	7 (7.6)
Nasopharyngitis	32 (14.5)	3 (3.3)
Pitting edema	32 (14.5)	9 (9.8)
Skin lesion	32 (14.5)	8 (8.7)
Dyspnea exertional	31 (14.1)	15 (16.3)
Injection site bruising	31 (14.1)	0
Rash	31 (14.1)	9 (9.8)
Injection site reaction	30 (13.6)	0
Anxiety	29 (13.2)	3 (3.3)
Appetite decreased	28 (12.7)	8 (8.7)
Fatigue aggravated	28 (12.7)	4 (4.3)
Hypokalemia	28 (12.7)	12 (13.0)
Upper respiratory tract infection	28 (12.7)	4 (4.3)
Pruritus	27 (12.3)	11 (12.0)
Abdominal tenderness	26 (11.8)	1 (1.1)
Depression	26 (11.8)	7 (7.6)
Productive cough	25 (11.4)	4 (4.3)
Insomnia	24 (10.9)	4 (4.3)
Malaise	24 (10.9)	1 (1.1)
Pain	24 (10.9)	3 (3.3)
Pneumonia	24 (10.9)	5 (5.4)
Abdominal pain upper	23 (10.5)	3 (3.3)
Crackles lung	23 (10.5)	8 (8.7)
Sweating increased	23 (10.5)	2 (2.2)
Cardiac murmur	22 (10.0)	8 (8.7)
Rhinorrhea	22 (10.0)	2 (2.2)
Gingival bleeding	21 (9.5)	4 (4.3)
Lymphadenopathy	21 (9.5)	3 (3.3)
Herpes simplex	20 (9.1)	5 (5.4)
Hematoma	19 (8.6)	0
Night sweats	19 (8.6)	3 (3.3)
Rales	19 (8.6)	8 (8.7)
Tachycardia	19 (8.6)	6 (6.5)
Wheezing	19 (8.6)	2 (2.2)
Cellulitis	18 (8.2)	4 (4.3)

Preferred Term[b]	All VIDAZA[c] (N=220)	Observation[d] (N=92)
At least 1 TEAE	219 (99.5)	89 (96.7)
Dysuria	18 (8.2)	2 (2.2)
Breath sounds decreased	17 (7.7)	1 (1.1)
Lethargy	17 (7.7)	2 (2.2)
Oral mucosal petechiae	17 (7.7)	3 (3.3)
Stomatitis	17 (7.7)	0
Urinary tract infection	17 (7.7)	5 (5.4)
Peripheral swelling	16 (7.3)	5 (5.4)
Dyspepsia	15 (6.8)	4 (4.3)
Hemorrhoids	15 (6.8)	1 (1.1)
Hypotension	15 (6.8)	2 (2.2)
Injection site pruritus	15 (6.8)	0
Transfusion reaction	15 (6.8)	0
Pleural effusion	14 (6.4)	6 (6.5)
Abdominal distension	13 (5.9)	4 (4.3)
Muscle cramps	13 (5.9)	3 (3.3)
Post procedural hemorrhage	13 (5.9)	1 (1.1)
Postnasal drip	13 (5.9)	3 (3.3)
Rhonchi	13 (5.9)	2 (2.2)
Syncope	13 (5.9)	5 (5.4)
Urticaria	13 (5.9)	1 (1.1)
Anemia aggravated	12 (5.5)	5 (5.4)
Loose stools	12 (5.5)	0
Nasal congestion	12 (5.5)	1 (1.1)
Atelectasis	11 (5.0)	2 (2.2)
Chest wall pain	11 (5.0)	0
Dry skin	11 (5.0)	1 (1.1)
Dysphagia	11 (5.0)	2 (2.2)
Dyspnea exacerbated	11 (5.0)	3 (3.3)
Hypoesthesia	11 (5.0)	1 (1.1)
Injection site granuloma	11 (5.0)	0
Injection site pigmentation changes	11 (5.0)	0
Injection site swelling	11 (5.0)	0
Mouth hemorrhage	11 (5.0)	1 (1.1)
Post procedural pain	11 (5.0)	2 (2.2)
Sinusitis	11 (5.0)	3 (3.3)
Skin nodule	11 (5.0)	1 (1.1)
Tongue ulceration	11 (5.0)	2 (2.2)

[a] Mean VIDAZA exposure = 11.4 months. Mean time in observation arm = 6.1 months.

[b] Multiple reports of the same preferred terms for a patient are only counted once within each treatment group.

[c] Includes events from all patients exposed to VIDAZA, including patients after crossing over from observation.

[d] Includes events from observation period only; excludes any events after crossover to VIDAZA.

For SC VIDAZA administration, nausea, vomiting, diarrhea, and constipation all tended to increase in incidence with increasing doses of VIDAZA. Nausea, vomiting, injection site erythema, constipation, rigors, petechiae, injection site pain, dizziness, injection site bruising, anxiety, hypokalemia, insomnia, epistaxis, and rales tended to be more pronounced during the first 1–2 cycles of SC VIDAZA treatment compared with later cycles of treatment. There did not appear to be any adverse events that increased in frequency over the course of treatment. There did not appear to be any relevant differences in adverse events by gender.

Overall, adverse reactions were qualitatively similar between the IV and SC studies. Adverse reactions that appeared to be specifically associated with the IV route of administration included infusion site reactions (e.g., erythema or pain) and catheter site reactions (e.g., infection, erythema, or hemorrhage).

In clinical studies of either SC or IV VIDAZA, the following serious treatment-related adverse events occurring at a rate of <5% (not described in Table 4) were reported:

Blood and lymphatic system disorders: agranulocytosis, bone marrow depression, splenomegaly.

Cardiac disorders: atrial fibrillation, cardiac failure, cardiac failure congestive, cardio-respiratory arrest, congestive cardiomyopathy.

Gastrointestinal disorders: diverticulitis, gastrointestinal hemorrhage, melena, perirectal abscess.

General disorders and administration site conditions: catheter site hemorrhage, general physical health deterioration, systemic inflammatory response syndrome.

Hepatobiliary disorders: cholecystitis.

Immune system disorders: anaphylactic shock, hypersensitivity.

Infections and infestations: abscess limb, bacterial infection, blastomycosis, injection site infection, Klebsiella sepsis, pharyngitis streptococcal, pneumonia Klebsiella, sepsis, Staphylococcal bacteremia, Staphylococcal infection, toxoplasmosis.

Metabolism and nutrition disorders: dehydration.

Musculoskeletal and connective tissue disorders: bone pain aggravated, muscle weakness, neck pain.

Neoplasms benign, malignant and unspecified: leukemia cutis.

Nervous system disorders: convulsions, intracranial hemorrhage.

Psychiatric disorders: confusion.

Renal and urinary disorders: hematuria, loin pain, renal failure.

Respiratory, thoracic and mediastinal disorders: hemoptysis, lung infiltration, pneumonitis, respiratory distress.

Skin and subcutaneous tissue disorders: pyoderma gangrenosum, rash pruritic, skin induration.

Surgical and medical procedures: cholecystectomy.

Vascular disorders: orthostatic hypotension.

OVERDOSAGE

One case of overdose with VIDAZA was reported during clinical trials. A patient experienced diarrhea, nausea, and vomiting after receiving a single IV dose of approximately 290 mg/m^2, almost 4 times the recommended starting dose. The events resolved without sequelae, and the correct dose was resumed the following day. 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 VIDAZA overdosage.

DOSAGE AND ADMINISTRATION

First Treatment Cycle

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology laboratory values, is 75 mg/m^2 subcutaneously or intravenously, daily for 7 days. Patients should be premedicated for nausea and vomiting.

Subsequent Treatment Cycles

Cycles should be repeated every 4 weeks. The dose may be increased to 100 mg/m^2 if no beneficial effect is seen after 2 treatment cycles and if no toxicity other than nausea and vomiting has occurred. It is recommended that patients be treated for a minimum of 4 cycles. However, complete or partial response may require more than 4 treatment cycles. Treatment may be continued as long as the patient continues to benefit.

Patients should be monitored for hematologic response and renal toxicities (see **PRECAUTIONS)**, and dosage delay or reduction as described below may be necessary.

Dosage Adjustment Based on Hematology Laboratory Values:

- For patients with baseline (start of treatment) WBC ≥3.0 x10^9/L, ANC ≥1.5 x10^9/L, and platelets ≥75.0 x10^9/L, adjust the dose as follows, based on nadir counts for any given cycle:

Nadir Counts		% Dose in the Next Course
ANC (x10^9/L)	Platelets (x10^9/L)	
<0.5	<25.0	50%
0.5–1.5	25.0–50.0	67%
>1.5	>50.0	100%

- For patients whose baseline counts are WBC <3.0 x10^9/L, ANC<1.5 x10^9/L, or platelets <75.0 x10^9/L, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

WBC or Platelet Nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir (%)		
	30–60	15–30	<15
	% Dose in the Next Course		
50–75	100	50	33
> 75	75	50	33

If a nadir as defined in the table above has occurred, the next course of treatment should be given 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are >25% above the nadir and rising. If a >25% increase above the nadir is not seen by day 28, counts should be reassessed every 7 days. If a 25% increase is not seen by day 42, then the patient should be treated with 50% of the scheduled dose.

Dosage Adjustment Based on Renal Function and Serum Electrolytes: If unexplained reductions in serum bicarbonate levels to less than 20 mEq/L occur, the dosage should be reduced by 50% on the next course. Similarly, if unexplained elevations of BUN or serum creatinine occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment course. (See **PRECAUTIONS**.)

Use in Geriatric Patients: Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **PRECAUTIONS**.)

Preparation of VIDAZA

VIDAZA is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing VIDAZA suspensions. (See **Handling and Disposal**.)

If reconstituted VIDAZA comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water.

The VIDAZA vial is single-use and does not contain any preservatives. Unused portions of each vial should be discarded properly. See **Handling and Disposal.** Do not save any unused portions for later administration.

Preparation for Subcutaneous Administration

VIDAZA should be reconstituted aseptically with 4 mL sterile water for injection. The diluent should be injected slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain azacitidine 25 mg/mL.

Preparation for Immediate Subcutaneous Administration: Doses greater than 4 mL should be divided equally into 2 syringes. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

Preparation for Delayed Subcutaneous Administration: The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into 2 syringes. The product must be refrigerated immediately, and may be held under refrigerated conditions (2ºC–8ºC, 36ºF–46ºF) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Subcutaneous Administration

To provide a homogeneous suspension, the contents of the syringe must be re-suspended by inverting the syringe 2–3 times and vigorously rolling the syringe between the palms for 30 seconds immediately prior to administration.

VIDAZA suspension is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh,

abdomen, or upper arm). New injections should be given at least 1 inch from an old site and never into areas where the site is tender, bruised, red, or hard.

Suspension Stability

VIDAZA reconstituted for subcutaneous administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F).

Preparation for Intravenous Administration

Reconstitute the appropriate number of VIDAZA vials to achieve the desired dose. Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Withdraw the required amount of VIDAZA solution to deliver the desired dose and inject into a 50-100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

Intravenous Solution Incompatibility

VIDAZA is incompatible with 5% Dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of VIDAZA and should therefore be avoided.

Intravenous Administration

VIDAZA solution is administered intravenously. Administer the total dose over a period of 10-40 minutes. The administration must be completed within 1 hour of reconstitution of the VIDAZA vial.

Solution Stability

VIDAZA reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

HOW SUPPLIED

VIDAZA (azacitidine for injection) is supplied as a lyophilized powder in 100 mg single-use vials packaged in cartons of 1 vial (NDC 67211-102-01).

Storage

Store unreconstituted vials at 25ºC (77ºF); excursions permitted to 15º–30ºC (59º–86ºF) (See USP Controlled Room Temperature.)

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be applied. Several guidelines on this subject have been published.[1–5] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

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