

## Brief Summary of Prescribing Information

Vidaza®  
(azacitidine for injectable suspension) **Rx** only

For subcutaneous use only

### 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<sup>2</sup> (approximately 8% of the recommended human daily dose on a mg/m<sup>2</sup> 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<sup>2</sup> (approximately 4%–16% the recommended human daily dose on a mg/m<sup>2</sup> basis).

In rats, azacitidine was clearly embryotoxic when given IP on gestation days 4–8 (postimplantation) at a dose of 6 mg/m<sup>2</sup> (approximately 8% of the recommended human daily dose on a mg/m<sup>2</sup> 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 to 12 mg/m<sup>2</sup> (approximately 8% the recommended human daily dose on a mg/m<sup>2</sup> basis) given on gestation day 9, 10, 11 or 12. In this study azacitidine caused fetal death when administered at 3–12 mg/m<sup>2</sup> 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, club foot, 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 pre-mating 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 section of full prescribing information.

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 pre-existing 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 non-MDS 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 section of full prescribing information.

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 of full prescribing information).

#### Information for Patients

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

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 section of full prescribing information.)

#### 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<sup>2</sup>, approximately 8% the recommended human daily dose on a mg/m<sup>2</sup> basis) administered IP three 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<sup>2</sup>, approximately 8% the recommended human daily dose on a mg/m<sup>2</sup> basis) once a week for 50 weeks. A tumorigenicity study in rats dosed twice weekly at 15 or 60 mg/m<sup>2</sup> (approximately 20–80% the recommended human daily dose on a mg/m<sup>2</sup> 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<sup>2</sup> (approximately 9% the recommended human daily dose on a mg/m<sup>2</sup> 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 three times per week for 11 or 16 weeks at doses of 15 to 30 mg/m<sup>2</sup> (approximately 20–40% the recommended human daily dose on a mg/m<sup>2</sup> 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<sup>2</sup> 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 section.

#### 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 three clinical studies described in CLINICAL STUDIES section of full prescribing information, 62 percent were 65 years and older and 21 percent 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 of full prescribing information).

### 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 Route):** nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, fatigue, injection site erythema, constipation, neutropenia, ecchymosis.

#### Adverse Reactions Most Frequently (>2%) Resulting in Clinical Intervention (SC 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 one 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<sup>2</sup>.

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)\***

Preferred Term**	All Vidaza† (N=220)	Observation† (N=92)
<b>At least 1 TEAE</b>	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)
Constipation	41 (18.6)	9 (9.8)
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)