HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIDAZA safely and effectively. See full prescribing information for VIDAZA.

VIDAZA (azacitidine for injection) for SC or IV use
Initial U.S. Approval: 2004

----------INDICATIONS AND USAGE----------

VIDAZA is a nucleoside metabolic inhibitor indicated for the treatment of patients with the following FAB myelodysplastic syndrome (MDS) subtypes: Refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL). (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology values, is VIDAZA 75 mg/m^2 daily for 7 days to be administered by subcutaneous (SC) injection or intravenous (IV) infusion. Premedicate for nausea and vomiting. (2.1)
- Repeat cycles every 4 weeks (2.2). After 2 cycles, may increase dose to 100 mg/m^2 if no beneficial effect is seen and no toxicity other than nausea and vomiting has occurred (2.2). Patients should be treated for a minimum of 4 to 6 cycles. Complete or partial response may require additional treatment cycles (2.2).
- Continue treatment as long as the patient continues to benefit (2.2).
- Patients should be monitored for hematologic response and renal toxicities, with dosage delay or reduction as appropriate (2.3, 2.4, 2.5).

----------DOSAGE FORMS AND STRENGTHS----------

- Lyophilized powder in 100 mg single-use vials (3).

----------CONTRAINDICATIONS----------

- Advanced malignant hepatic tumors (4.1).
- Hypersensitivity to azacitidine or mannitol (4.2).

----------WARNINGS AND PRECAUTIONS----------

- Anemia, neutropenia and thrombocytopenia. Perform complete blood counts (CBC) prior to each treatment cycle and as needed to monitor response and toxicity. (5.1).
- Hepatotoxicity: Use with caution in patients with severe preexisting liver impairment (5.2).
- Renal abnormalities. Monitor patients with renal impairment for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys (5.3).
- Monitor liver chemistries and serum creatinine prior to initiation of therapy and with each cycle (5.4).
- VIDAZA may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be apprised of the potential hazard to a fetus. (5.5, 8.1).
- Men should be advised not to father a child while receiving VIDAZA (5.6, 13).

----------ADVERSE REACTIONS----------

Most common adverse reactions (>30%) by SC route are: nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia and ecchymosis. Most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- No formal assessments of drug-drug interactions between VIDAZA and other agents have been conducted (7).

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3).
- Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function (8.5).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: August 2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Myelodysplastic Syndromes (MDS)

VIDAZA® is indicated for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).

2 DOSAGE AND ADMINISTRATION

2.1 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.

2.2 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 to 6 cycles. However, complete or partial response may require additional 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 Warnings and Precautions (5.3)]*, and dosage delay or reduction as described below may be necessary.

2.3 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.

2.4 Dosage Adjustment Based on Renal Function and Serum Electrolytes

If unexplained reductions in serum bicarbonate levels to <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 Warnings and Precautions (5.3)]*.

2.5 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 Warnings and Precautions (5.3) and Use in Specific Populations (8.5*)].

2.6 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 How Supplied/Storage and Handling (16)]*.

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 How Supplied/Storage and Handling (16)]*. Do not save any unused portions for later administration.

2.7 Instructions 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 dosing syringe must be re-suspended immediately prior to administration. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved.

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 one 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).

2.8 Instructions 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 10 mg/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.

3 DOSAGE FORMS AND STRENGTHS

VIDAZA (azacitidine for injection) is supplied as lyophilized powder in 100 mg single-use vials.

4 CONTRAINDICATIONS

4.1 Advanced Malignant Hepatic Tumors

VIDAZA is contraindicated in patients with advanced malignant hepatic tumors *[see Warnings and Precautions (5.2)]*.

4.2 Hypersensitivity to Azacitidine or Mannitol

VIDAZA is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol.

5 WARNINGS AND PRECAUTIONS

5.1 Anemia, Neutropenia and Thrombocytopenia

Treatment with VIDAZA is associated with anemia, 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 *[see Dosage and Administration (2.3)]*.

5.2 Severe Preexisting Hepatic Impairment

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 (4.1)]*.

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

5.3 Renal Abnormalities

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 *[see Dosage and Administration (2.4)]*.

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 (2.4, 2.5)]*.

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

5.4 Monitoring 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.

5.5 Pregnancy

Pregnancy Category D

VIDAZA may cause fetal harm when administered to a pregnant woman. Azacitidine caused congenital malformations in animals. Women of childbearing potential should be advised to avoid pregnancy during treatment with VIDAZA. There are no adequate and well-controlled studies in pregnant women using VIDAZA. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5.6 Use in Males

Men should be advised to not father a child while receiving treatment with VIDAZA. In animal studies, pre-conception treatment of male mice and rats resulted in increased embryofetal loss in mated females *[see Nonclinical Toxicology (13)]*.

6 ADVERSE REACTIONS

6.1 Overview

Adverse Reactions Described in Other Labeling Sections: anemia, neutropenia, thrombocytopenia, elevated serum creatinine, renal failure, renal tubular acidosis, hypokalemia, hepatic coma *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Most Commonly Occurring Adverse Reactions (SC or IV Route): nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, 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, thrombocytopenia, neutropenia.
Dose Held: leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia.
Dose Reduced: leukopenia, neutropenia, thrombocytopenia.

6.2 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to VIDAZA in 443 MDS patients from 4 clinical studies. Study 1 was a supportive-care controlled trial (SC administration), Studies 2 and 3 were single arm studies (one with SC administration and one with IV administration), and Study 4 was an international randomized trial (SC administration) *[see Clinical Studies (14)]*.

In Studies 1, 2 and 3, a total of 268 patients were exposed to VIDAZA, 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^2.

In Study 4, a total of 175 patients with higher-risk MDS (primarily RAEB and RAEB-T subtypes) were exposed to VIDAZA. Of these patients, 119 were exposed for 6 or more cycles, and 63 for at least 12 cycles. The mean age of this population was 68.1 years (ranging from 42 to 83 years), 74% were male, and 99% were white. Most patients received daily VIDAZA doses of 75 mg/m^2.

Table 1 presents adverse reactions occurring in at least 5% of patients treated with VIDAZA (SC) in Studies 1 and 2. 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 1: Most Frequently Observed Adverse Reactions (≥ 5.0% in All SC VIDAZA Treated Patients; Studies 1 and 2)

	Number (%) of Patients			
System Organ Class Preferred Term[a]	**All VIDAZA[b] (N=220)**		**Observation[c] (N=92)**	
Blood and lymphatic system disorders				
Anemia	153	(69.5)	59	(64.1)
Anemia aggravated	12	(5.5)	5	(5.4)
Febrile neutropenia	36	(16.4)	4	(4.3)
Leukopenia	106	(48.2)	27	(29.3)
Neutropenia	71	(32.3)	10	(10.9)
Thrombocytopenia	144	(65.5)	42	(45.7)
Gastrointestinal disorders				
Abdominal tenderness	26	(11.8)	1	(1.1)
Constipation	74	(33.6)	6	(6.5)
Diarrhea	80	(36.4)	13	(14.1)
Gingival bleeding	21	(9.5)	4	(4.3)
Loose stools	12	(5.5)	0	
Mouth hemorrhage	11	(5.0)	1	(1.1)
Nausea	155	(70.5)	16	(17.4)
Stomatitis	17	(7.7)	0	
Vomiting	119	(54.1)	5	(5.4)
General disorders and administration site conditions				
Chest pain	36	(16.4)	5	(5.4)
Injection site bruising	31	(14.1)	0	
Injection site erythema	77	(35.0)	0	
Injection site granuloma	11	(5.0)	0	
Injection site pain	50	(22.7)	0	
Injection site pigmentation changes	11	(5.0)	0	
Injection site pruritus	15	(6.8)	0	
Injection site reaction	30	(13.6)	0	
Injection site swelling	11	(5.0)	0	
Lethargy	17	(7.7)	2	(2.2)
Malaise	24	(10.9)	1	(1.1)
Pyrexia	114	(51.8)	28	(30.4)

Table 1: Most Frequently Observed Adverse Reactions (≥ 5.0% in All SC VIDAZA Treated Patients; Studies 1 and 2)

	Number (%) of Patients	
System Organ Class **Preferred Term[a]**	**All VIDAZA[b] (N=220)**	**Observation[c] (N=92)**
Infections and infestations		
Nasopharyngitis	32 (14.5)	3 (3.3)
Pneumonia	24 (10.9)	5 (5.4)
Upper respiratory tract infection	28 (12.7)	4 (4.3)
Injury, poisoning, and procedural complications		
Post procedural hemorrhage	13 (5.9)	1 (1.1)
Metabolism and nutrition disorders		
Anorexia	45 (20.5)	6 (6.5)
Musculoskeletal and connective tissue disorders		
Arthralgia	49 (22.3)	3 (3.3)
Chest wall pain	11 (5.0)	0
Myalgia	35 (15.9)	2 (2.2)
Nervous system disorders		
Dizziness	41 (18.6)	5 (5.4)
Headache	48 (21.8)	10 (10.9)
Psychiatric disorders		
Anxiety	29 (13.2)	3 (3.3)
Insomnia	24 (10.9)	4 (4.3)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	64 (29.1)	11 (12.0)
Skin and subcutaneous tissue disorders		
Dry skin	11 (5.0)	1 (1.1)
Ecchymosis	67 (30.5)	14 (15.2)
Erythema	37 (16.8)	4 (4.3)
Rash	31 (14.1)	9 (9.8)
Skin nodule	11 (5.0)	1 (1.1)
Urticaria	13 (5.9)	1 (1.1)
Vascular disorders		
Hematoma	19 (8.6)	0
Hypotension	15 (6.8)	2 (2.2)
Petechiae	52 (23.6)	8 (8.7)

[a] Multiple terms of the same preferred terms for a patient are only counted once within each treatment group.
[b] Includes adverse reactions from all patients exposed to VIDAZA, including patients after crossing over from observations.
[c] Includes adverse reactions from observation period only; excludes any adverse events after crossover to VIDAZA.

Table 2 presents adverse reactions occurring in at least 5% of patients treated with VIDAZA in Study 4. Similar to Studies 1 and 2 described above, duration of exposure to treatment with VIDAZA was longer (mean 12.2 months) compared with best supportive care (mean 7.5 months).

Table 2: Most Frequently Observed Adverse Reactions (≥ 5.0% in the VIDAZA Treated Patients and the Percentage with NCI CTC Grade 3/4 Reactions; Study 4)

	Number (%) of Patients			
	Any Grade		Grade 3/4	
System Organ Class Preferred Term[a]	VIDAZA (N=175)	Best Supportive Care Only (N=102)	VIDAZA (N=175)	Best Supportive Care Only (N=102)
Blood and lymphatic system disorders				
Anemia	90 (51.4)	45 (44.1)	24 (13.7)	9 (8.8)
Febrile neutropenia	24 (13.7)	10 (9.8)	22 (12.6)	7 (6.9)
Leukopenia	32 (18.3)	2 (2.0)	26 (14.9)	1 (1.0)
Neutropenia	115 (65.7)	29 (28.4)	107 (61.1)	22 (21.6)
Thrombocytopenia	122 (69.7)	35 (34.3)	102 (58.3)	29 (28.4)
Gastrointestinal disorders				
Abdominal pain	22 (12.6)	7 (6.9)	7 (4.0)	0
Constipation	88 (50.3)	8 (7.8)	2 (1.1)	0
Dyspepsia	10 (5.7)	2 (2.0)	0	0
Nausea	84 (48.0)	12 (11.8)	3 (1.7)	0
Vomiting	47 (26.9)	7 (6.9)	0	0
General disorders and administration site conditions				
Fatigue	42 (24.0)	12 (11.8)	6 (3.4)	2 (2.0)
Injection site bruising	9 (5.1)	0	0	0
Injection site erythema	75 (42.9)	0	0	0
Injection site hematoma	11 (6.3)	0	0	0
Injection site induration	9 (5.1)	0	0	0
Injection site pain	33 (18.9)	0	0	0
Injection site rash	10 (5.7)	0	0	0
Injection site reaction	51 (29.1)	0	1 (0.6)	0
Pyrexia	53 (30.3)	18 (17.6)	8 (4.6)	1 (1.0)
Infections and infestations				
Rhinitis	10 (5.7)	1 (1.0)	0	0
Upper respiratory tract infection	16 (9.1)	4 (3.9)	3 (1.7)	0
Urinary tract infection	15 (8.6)	3 (2.9)	3 (1.7)	0
Investigations				
Weight decreased	14 (8.0)	0	1 (0.6)	0
Metabolism and nutrition disorders				
Hypokalemia	11 (6.3)	3 (2.9)	3 (1.7)	3 (2.9)
Nervous system disorders				
Lethargy	13 (7.4)	2 (2.0)	0	1 (1.0)
Psychiatric disorders				
Anxiety	9 (5.1)	1 (1.0)	0	0
Insomnia	15 (8.6)	3 (2.9)	0	0
Renal and urinary disorders				
Hematuria	11 (6.3)	2 (2.0)	4 (2.3)	1 (1.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	26 (14.9)	5 (4.9)	6 (3.4)	2 (2.0)
Dyspnea exertional	9 (5.1)	1 (1.0)	0	0
Pharyngolaryngeal pain	11 (6.3)	3 (2.9)	0	0
Skin and subcutaneous tissue disorders				
Erythema	13 (7.4)	3 (2.9)	0	0
Petechiae	20 (11.4)	4 (3.9)	2 (1.1)	0
Pruritus	21 (12.0)	2 (2.0)	0	0
Rash	18 (10.3)	1 (1.0)	0	0
Vascular disorders				
Hypertension	15 (8.6)	4 (3.9)	2 (1.1)	2 (2.0)

[a] Multiple reports of the same preferred term from a patient were only counted once within each treatment.

In Studies 1, 2 and 4 with SC administration of VIDAZA, adverse reactions of neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, constipation, and injection site erythema/reaction tended to increase in incidence with higher doses of VIDAZA. Adverse reactions that tended to be more pronounced during the first 1 to 2 cycles of SC treatment compared with later cycles included thrombocytopenia, neutropenia, anemia, nausea, vomiting, injection site erythema/pain/bruising/reaction, constipation, petechiae, dizziness, anxiety, hypokalemia, and insomnia. There did not appear to be any adverse reactions that increased in frequency over the course of treatment.

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 adverse reactions occurring at a rate of < 5% (and not described in Tables 1 or 2) were reported:

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

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

Eye disorders: eye hemorrhage

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, cellulitis, blastomycosis, injection site infection, Klebsiella sepsis, neutropenic sepsis, pharyngitis streptococcal, pneumonia Klebsiella, sepsis, septic shock, 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: cerebral hemorrhage, convulsions, intracranial hemorrhage.

Renal and urinary disorders: 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.

6.3 Postmarketing Experience

Adverse reactions identified from spontaneous reports have been similar to those reported during clinical trials with VIDAZA.

7 DRUG INTERACTIONS

No formal assessments of drug-drug interactions between VIDAZA and other agents have been conducted *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D
VIDAZA may cause fetal harm when administered to a pregnant woman. Azacitidine was teratogenic in animals. Women of childbearing potential should be advised to avoid pregnancy during treatment with VIDAZA. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Female partners of male patients receiving VIDAZA should not become pregnant *[see Nonclinical Toxicology (13)]*.

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 to 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, club foot, syndactyly, oligodactyly), and others (micrognathia, gastroschisis, edema, and rib abnormalities).

8.3 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 in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in Studies 1, 2 and 3, 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 reactions observed in patients 65 years and older compared to younger patients.

Of the 179 patients randomized to azacitidine in Study 4, 68% were 65 years and older and 21% were 75 years and older. Survival data for patients 65 years and older were consistent with overall survival results. The majority of adverse reactions occurred at similar frequencies in patients < 65 years of age and patients 65 years of age and older.

Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of adverse 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 (2.5) and Warnings and Precautions (5.3)]*.

8.6 Gender

There were no clinically relevant differences in safety and efficacy based on gender.

8.7 Race

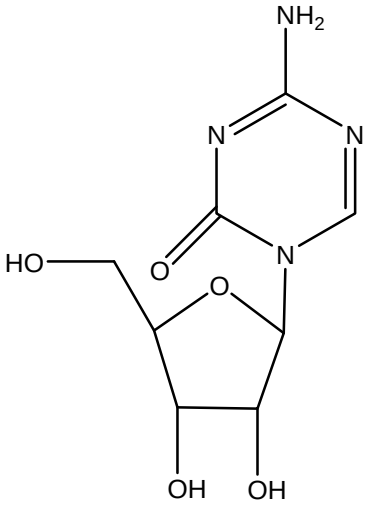
Greater than 90% of all patients in all trials were Caucasian. Therefore, no comparisons between Caucasians and non-Caucasians were possible.

10 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.

11 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 mannitol as a sterile lyophilized powder.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VIDAZA is a pyrimidine nucleoside analog of cytidine. 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. Non-proliferating cells are relatively insensitive to azacitidine.

12.3 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 Dosage and Administration (2.4), Contraindications (4.1) and Warnings and Precautions (5.2, 5.3)]*.

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.

13 NONCLINICAL TOXICOLOGY

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 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^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.

14 CLINICAL STUDIES

Myelodysplastic Syndromes (MDS)

Study 1 was 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 five 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. Supportive care allowed in this study included blood transfusion products, antibiotics, antiemetics, analgesics and antipyretics. The use of hematopoeitic growth factors was prohibited. Baseline patient and disease characteristics are summarized in Table 3; 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 4).

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 3. 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 4. 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 5). 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 5. 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%.

Study 2, 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 Study 3, 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.

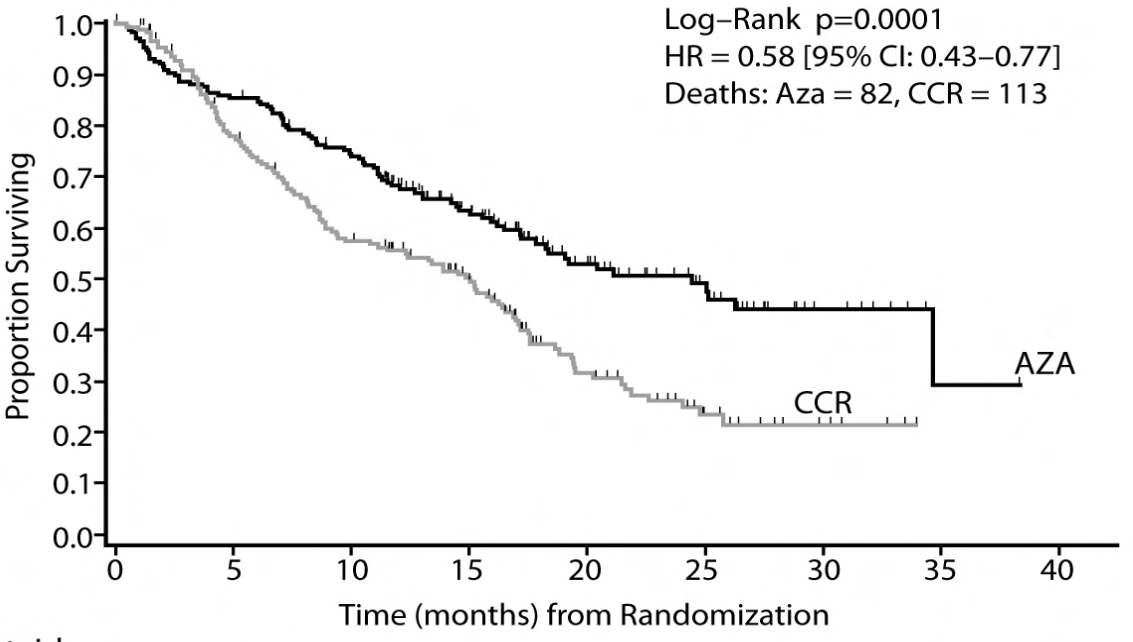
Study 4 was an international, multicenter, open-label, randomized trial in MDS patients with RAEB, RAEB-T or modified CMMoL according to FAB classification and Intermediate-2 and High risk according to IPSS classification. Of the 358 patients enrolled in the study, 179 were randomized to receive azacitidine plus best supportive care (BSC) and 179 were randomized to receive conventional care regimens (CCR) plus BSC (105 to BSC alone, 49 to low dose cytarabine and 25 to chemotherapy with cytarabine and anthracycline). The primary efficacy endpoint was overall survival.

The azacitidine and CCR groups were comparable for baseline parameters. The median age of patients was 69 years (range was 38-88 years), 98% were Caucasian, and 70% were male. At baseline, 95% of the patients were higher risk by FAB classification: RAEB (58%), RAEB-T (34%), and CMMoL (3%). By IPSS classification, 87% were higher risk: Int-2 (41%), High (47%). At baseline, 32% of patients met WHO criteria for AML.

Azacitidine was administered subcutaneously at a dose of 75 mg/m^2 daily for 7 consecutive days every 28 days (which constituted one cycle of therapy). Patients continued treatment until disease progression, relapse after response, or unacceptable toxicity. Azacitidine patients were treated for a median of 9 cycles (range 1 to 39), BSC only patients for a median of 7 cycles (range 1 to 26), low dose cytarabine patients for a median of 4.5 cycles (range 1 to 15), and chemotherapy with cytarabine and anthracycline patients for a median of 1 cycle (range 1 to 3, i.e. induction plus 1 or 2 consolidation cycles).

In the Intent-to-Treat analysis, patients treated with azacitidine demonstrated a statistically significant difference in overall survival as compared to patients treated with CCR (median survival of 24.5 months vs. 15.0 months; stratified log-rank p=0.0001). The hazard ratio describing this treatment effect was 0.58 (95% CI: 0.43, 0.77).

Kaplan-Meier Curve of Time to Death from Any Cause: (Intent-to-Treat Population)



# at risk									
AZA	179	152	130	85	52	30	10	1	0
CCR	179	132	95	69	32	14	5	0	0

Key: AZA = azacitidine ; CCR = conventional care regimens; CI = confidence interval; HR = Hazard Ratio

Azacitidine treatment led to a reduced need for red blood cell transfusions (see Table 6). In patients treated with azacitidine who were RBC transfusion dependent at baseline and became transfusion independent, the median duration of RBC transfusion independence was 13.0 months.

Table 6. Effect of Azacitidine on RBC Transfusions in MDS Patients

Efficacy Parameter	Azacitidine plus BSC (n= 179)	Conventional Care Regimens (n= 179)
Number and percent of patients who were transfusion dependent at baseline who became transfusion independent on treatment[1]	50/111 (45.0%)	13/114 (11.4%)
	(95% CI: 35.6%, 54.8%)	(95% CI: 6.2%, 18.7%)
Number and percent of patients who were transfusion-independent at baseline who became transfusion-dependent on treatment	10/68 (14.7%)	28/65 (43.1%)
	(95% CI: 7.3%, 25.4%)	(95% CI: 30.9%, 56.0%)

[1]A patient was considered RBC transfusion independent during the treatment period if the patient had no RBC transfusions during any 56 consecutive days or more during the treatment period. Otherwise, the patient was considered transfusion dependent.

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. (2006) 63:1172-1193.

4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 59572-102-01).

Storage

Store unreconstituted vials at 25º C (77º F); excursions permitted to 15º-30º C (59º-86º F) (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.[1-4] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

17 PATIENT COUNSELING INFORMATION

Instruct patients to inform their physician about any underlying liver or renal disease.

Advise women of childbearing potential to avoid becoming pregnant while receiving treatment with VIDAZA. For nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother.

Advise men not to father a child while receiving treatment with VIDAZA.

Manufactured for: Celgene Corporation
Summit, NJ 07901

Manufactured by: Ben Venue Laboratories, Inc.
Bedford, OH 44146

Or

Baxter Oncology GmbH
33790 Halle/Westfalen Germany